













NEW AND  
NONOFFICIAL REMEDIES  
1954

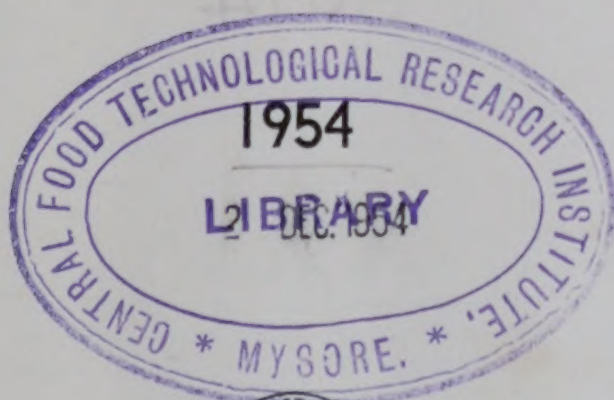




# *New and Nonofficial* **REMEDIES**

CONTAINING DESCRIPTIONS OF THE ARTICLES  
WHICH STAND ACCEPTED BY THE COUNCIL  
ON PHARMACY AND CHEMISTRY OF THE  
AMERICAN MEDICAL ASSOCIATION ON  
JANUARY 1, 1954

*Issued Under the Direction and Supervision of*  
The Council on Pharmacy and Chemistry  
American Medical Association



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## Preface

*New and Nonofficial Remedies* is published annually under the direction and supervision of the Council on Pharmacy and Chemistry of the American Medical Association. Included are articles which the Council has found acceptable under its rules through the period ending January 1 of the year of publication.

Many inquiries directed to the Council office reveal various misconceptions concerning the procedure for admission of articles to *New and Nonofficial Remedies*. The Council does not consider new drugs for inclusion in *New and Nonofficial Remedies* automatically on their release for commercial distribution. Submission of articles for consideration by the Council is accomplished entirely upon the voluntary initiative of the various pharmaceutical firms. The contents of *New and Nonofficial Remedies* reflect the confidence and faith of firms in the therapeutic worth of their products and in their ability to submit satisfactory evidence in support of the claims made for the articles.

Before the 1953 edition, *New and Nonofficial Remedies* consisted essentially of two principal sections. The first section contained general statements and monographs describing actions, uses, and dosages of various drugs; the second section contained tests and standards for Council accepted drugs for which official standards are not available. Henceforth, these two sections will appear as separate volumes, *New and Nonofficial Remedies* (containing material formerly in Section A, the Bibliography of Unaccepted Products, and Index to Distributors), and *Tests and Standards for New and Nonofficial Remedies* (formerly Section B). The decision to split the book was made after a survey indicated that interest in the book was either medical or pharmaceutical; few users found it necessary to utilize both sections to meet their particular needs. Because of the limited distribution of *Tests and Standards*, the Council decided to publish this volume at 3-year to 5-year intervals rather than annually. Information on the tests and standards for products examined by the A.M.A. Laboratories but not yet published in *Tests and Standards* is available from the Council office upon request.

Previous to the 1954 edition, *New and Nonofficial Remedies* contained a section entitled Bibliography of Unaccepted Products. The purpose of this section was to provide a convenient reference to those products that did not stand accepted by the Council. The Council decided to discontinue publication of this section for several reasons. Prominent among these reasons were that most of the products listed long since have been dropped from the drug market and several drugs formerly listed as unacceptable subsequently were accepted after the cause of the Council's original

objections was rectified. Those interested in the Council's opinion on old and new drugs not listed in *New and Nonofficial Remedies* may consult the bibliography in the 1953 edition (or previous editions) or write directly to the Secretary of the Council at A.M.A. headquarters.

In order to keep pace with changes in therapeutics, *New and Nonofficial Remedies* is reviewed annually by the Council to revise the general statements and monographs and to eliminate those articles no longer considered useful. *New and Nonofficial Remedies* provides the physician with such information concerning the actions, usage, limitations, and dosage of acceptable and relatively new drugs as will promote the practice of rational therapeutics. An innovation for the 1954 edition of *New and Nonofficial Remedies* is the publication of a list of the drugs omitted since the previous edition of the book and a list of the new drugs added.

Criticism of *New and Nonofficial Remedies* is invited with a view to further improvements of the book.

Acknowledgment is made of the assistance of Beverly Rodgers, Melvin Dupont, Paul L. Wermer, M.D., Secretary of the Committee on Publications, and personnel of the Chemical Section of the A.M.A. Laboratories.

ROBERT T. STORMONT, M.D., *Secretary*



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## Drugs Added to N.N.R. 1954

The drugs listed below were accepted by the Council in 1953 for inclusion in N.N.R.

Absorbable Gelatin Film (Gelfilm)  
 Anti-Hemophilic Plasma  
 Aurothioglycanide (Lauron)  
 Benzathine Penicillin G (Bicillin)  
 Carbomycin (Magnamycin)  
 Chlormerodrin (Neohydrin)  
 Chloroprocaine Penicillin O (Depo-Cer-O-Cillin  
     Chloroprocaine)  
 Cyclopentolate Hydrochloride (Cyclogyl Hydrochloride)  
 Dextran (Expandex, Gentran, Plavolex)  
 Dimethyl-Tubocurarine Chloride (Mecostrin Chloride)  
 Disulfiram (Antabuse)  
 Edrophonium Chloride (Tensilon Chloride)  
 Erythromycin (Ilotycin)  
 Erythromycin Stearate (Erythrocin Stearate)  
 Fructose (Levugen)  
 Hexamethonium Bromide (Bistrium Bromide)  
 Histamine Phosphate  
 Hydralazine Hydrochloride (Apresoline Hydrochloride)  
 Hydrocortisone (Cortef, Hydrocortone)  
 Levorphan Tartrate (Levo-Dromoran Tartrate)  
 Methoxamine Hydrochloride (Vasoxyl Hydrochloride)  
 Methylergonovine Tartrate (Methergine Tartrate)  
 Neomycin Sulfate (Mycifradin Sulfate)  
 Nitrofurantoin (Furadantin)  
 Phenindione (Danilone, Hedulin)  
 Phentolamine Hydrochloride (Regitine Hydrochloride)  
 Phentolamine Methanesulfonate (Regitine Methanesulfonate)  
 Protoveratrines A and B (Veralba)  
 Quinine Carbacrylic Resin (Diagnex)  
 Stilbamidine Isethionate  
 Succinylcholine Chloride (Anectine Chloride,  
     Quelicin Chloride)  
 Testosterone (Androlin)  
 Tetraethylammonium Chloride (Etamon Chloride)  
 Tolonium Chloride (Blutene Chloride)  
 Trihexyphenidyl Hydrochloride (Artane Hydrochloride)  
 Vitamin B<sub>12</sub> with Intrinsic Factor Concentrate (Bifactor)  
 Zincasate Burn Dressing (Zinax Burn Dressing)  
 Zinchlorundesal (Salundek, New)

## Drugs Omitted from N.N.R. 1954

The drugs listed below appeared in N.N.R. 1953 but do not appear in the present edition because they now are considered either sufficiently well known to warrant their exclusion or because they no longer are considered useful by the Council. Well-known drugs that are considered useful are listed in the index of N.N.R. with a reference to the last edition in which their actions and uses appeared.

Acriflavine-Brilliant Green-Methylrosaniline Chloride Mixture (Dymixal)†

Brucella Vaccine

Dehydrocholic Acid-U.S.P. (Decholin)

Furthrethonium Iodide (Furmethide Iodide)‡

Halibut Liver Oil with Viosterol (Haliver Oil with Viosterol)

Iodinated Castor Oil (Riodine)

Iodobrassid (Lipoiodine)

Racemorphan Hydrobromide (Dromoran Hydrobromide)\*

Sodium Dehydrocholate (Decholin Sodium)

Zincundesal (Salundek)\*

\* Racemorphan Hydrobromide and Zincundesal were replaced by Levorphan Tartrate and Zinchlorundesal, respectively, at the request of their manufacturers because evidence indicated that the new forms were superior in therapeutic efficacy.

† Acriflavine-Brilliant Green-Methylrosaniline Chloride Mixture and Furthrethonium Iodide were omitted from N.N.R. because the manufacturers of the only Council accepted dosage forms of these products discontinued their manufacture.



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## Purposes and Activities of the Council on Pharmacy and Chemistry

The Council on Pharmacy and Chemistry was created in 1905 as a standing committee, appointed by the Board of Trustees of the American Medical Association to consider medicinal and allied preparations offered for prophylactic, diagnostic, or therapeutic use by the physician.

The primary purpose of the Council is to encourage the practice of rational therapeutics. To achieve this objective the Council prepares special treatises, articles, status reports, and books designed to give authoritative information on therapeutics to the medical profession. The Council also encourages research in therapeutics by giving grants-in-aid, by arranging therapeutic trials of promising new preparations, and by stimulating basic research on fundamental problems.

It is recognized that the public has a legal right to practice self-medication, but the Council believes that only certain products may be so used with reasonable safety and intelligence. These products are defined in the rules.

In general the Council disapproves of the advertising of medicinal preparations to the public for treatment of disease conditions for the obvious reason that it promotes dangerous self-medication. Misdirected and inadequate treatment, both internal and external, failure to recognize serious disease until too late for effective treatment, the spread of infectious disease when hidden from the physician, description of symptoms in advertising leading to erroneous self-diagnosis, unconscious formation of drug habit, and the possibilities of inducing allergic and other undesirable reactions of the skin and other organs are potential hazards created by inadvisable self-treatment. These dangers apply similarly to the naming of diseases and therapeutic indications on labels which may fall into the hands of the patient. However, the Council recognizes that certain label instructions are necessary for the safe and proper use of those articles defined in the rules as safe to advertise to the public.



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## OFFICIAL RULES GOVERNING THE ADMISSION OF ARTICLES AND EXPLANATORY COMMENTS

The principles and policies of the Council which govern the acceptance of articles for inclusion in *New and Nonofficial Remedies* are expressed in the following Official Rules and Explanatory Comments. Acceptance of an article by the Council is not to be interpreted as either an endorsement or a recommendation for its use; it means merely that the product has been found to conform to the Council's rules.

Accepted products whose promotion, usefulness, or quality brings them in conflict with the rules are subject to withdrawal of acceptance and omission from *New and Nonofficial Remedies*.

### Rules Governing Acceptance

**RULE I.—Scope.**—*Any medicinal article which, in the judgment of the Council, is considered useful in the treatment, prevention or diagnosis of human disease is eligible for consideration for inclusion in New and Nonofficial Remedies.*

**Compliance with Laws.**—The responsibility for compliance with federal, state and municipal laws and regulations rests with the firm submitting an article.

**Commercial Availability.**—An article must be commercially available in the United States to be eligible for inclusion in *New and Nonofficial Remedies*, but articles may be submitted for preliminary consideration before they are made available to the medical profession.

**Mixtures.**—Mixtures of drugs are eligible for inclusion in *New and Nonofficial Remedies* providing they meet the requirements listed on page xxx under Criteria for the Evaluation of Certain Products.

**Experimental and Dangerous Drugs.**—Articles which have only experimental usefulness or whose use involves dangers and disadvantages outweighing their therapeutic value are considered ineligible for inclusion in *New and Nonofficial Remedies*.

**Bulk Drugs.**—Accepted drugs marketed in bulk for compounding prescriptions are eligible for inclusion in *New and Nonofficial Remedies*. Accepted drugs supplied in bulk form for manufacturing use only may be included in *New and Nonofficial Remedies*; but should such drugs become official, the bulk forms will be deleted from *New and Nonofficial Remedies*. Such acceptance should not be construed as extending to dosage forms of the accepted drug intended for distribution to physicians.

**Rejected Drugs.**—Previous noncompliance with the rules does not

preclude favorable consideration of an article at a later date if adequate evidence to overcome the original objections is submitted.

**Official and Nonofficial Drugs.**—An official drug is described in either the *U. S. Pharmacopeia* or the *National Formulary*; a non-official drug is not so described.

**Re-evaluation.**—An accepted or exempted drug may be re-evaluated by the Council at any time for compliance with existing rules and usefulness in medicine.

**Exemption of Well-Known Drugs.**—When the actions, uses and dosage of any drug become sufficiently well known in the opinion of the Council to make a full description in *New and Nonofficial Remedies* unnecessary for the information of the medical profession, the article may be declared exempt from further description. This does not apply if new uses of the drug or special methods of administration are introduced, which in the opinion of the Council justify discussion in the current N.N.R. In such cases, the drug or the special dosage form may be retained or restored to N.N.R. for an additional period not to exceed five years. If the novelty applies only to the dosage form, the discussion will be restricted to this form, with reference to the last edition containing a general discussion of the drug.

**Exemption of Official Drugs.**—Drugs in the *U. S. Pharmacopeia* or *National Formulary* or their equivalents automatically become exempt at the expiration of 20 years' inclusion in either of the official publications or in *New and Nonofficial Remedies*. The 20 year period is computed from the year when the drug was first included in one of these three publications.

**Re-evaluation of Nonofficial Drugs.**—Nonofficial drugs automatically become subject to re-evaluation on the same basis as newly submitted drugs at the expiration of 20 years' inclusion in *New and Nonofficial Remedies*. Firms are required to submit evidence of continued usefulness in medicine for products of their manufacture.

**Exemption of Re-evaluated Nonofficial Drugs.**—Re-evaluated non-official drugs which are considered still useful in the opinion of the Council shall be exempted as sufficiently well known. When exempted, nonofficial drugs will be retained in *Tests and Standards for New and Nonofficial Remedies*, but their actions, uses and dosage monographs will be deleted. When re-evaluated drugs are considered no longer useful, all information on them is subject to omission from *New and Nonofficial Remedies*.

**Brand and Generic Names of Exempt Drugs.**—The brand and generic names for exempt drugs will be listed in the general index with a reference to the last edition of *New and Nonofficial Remedies* in which actions, uses and dosage are described.

**Change in Official Status.**—Accepted or exempted articles containing drugs which are deleted from the *U. S. Pharmacopeia* or *National Formulary* are automatically subject to re-evaluation by the Council.

**Ineligible Articles.**—The Council does not consider for inclusion in *New and Nonofficial Remedies* articles which do not have direct medicinal significance, for example:



1. Chemical reagents and such insecticides, disinfectants and other substances as are not employed in or on the human body
2. Soaps or detergents for simple cleansing purposes
3. Surgical and hospital supplies, instruments or mechanical devices, appliances and other nonmedicinal articles.

**RULE 2.—Evidence.**—*Evidence of usefulness satisfactory to the Council must be presented for each new article submitted or for new or extended claims for accepted products.*

**Responsibility for Evidence.**—The firm which submits a new product or presents a new or extended claim for an acceptable or previously rejected product must bear the responsibility of supplying acceptable evidence to support the proposed claims.

#### **Amount and Type of Evidence Required**

**New Articles.**—For new articles, both animal and clinical data should be supplied. The plan of study, the number of observations, animals and patients should be such as to permit sound conclusions with respect to proposed clinical uses. The quality of evidence is quite as important as the quantity and in this respect the importance of suitable controls is emphasized. Statistical methods for designing the plan of study and for analyzing data should be employed when they are applicable. Particularly in clinical studies where interpretations are based on subjective evidence, supporting or confirming evidence from independent groups of investigators may be necessary.

**Previously Accepted Articles.**—Additional brands of articles included in *New and Nonofficial Remedies* or their equivalent counterparts are eligible for consideration without presentation of evidence when the claims do not exceed those recognized by the Council as published in *New and Nonofficial Remedies*. However, salts or esters of an accepted drug may be regarded in some instances as new articles.

Before new or extended claims or changes in dosage of accepted or exempt products may be made, evidence adequate to cover all proposed uses or changes should be submitted and found acceptable by the Council.

**RULE 3.—Composition.**—*The composition of articles submitted for inclusion in New and Nonofficial Remedies must be stated quantitatively whenever possible, with the understanding that complete formulas or their essential portions are subject to publication by the Council.*

**Secrecy.**—Physicians should know what they are prescribing. Unrevealed formulas or methods of treatment hamper the advance of scientific medicine and such practice cannot be defended as a means to protect a discovery. Therefore, the Council will not accept any product, the composition of which is not revealed.

**Label Requirements.**—Labels for submitted preparations must bear information to indicate the quantity of the active ingredients. Separately marketed topical vehicles should be labeled to indicate

the quantity of each of the major components, including those which may exert any local effect upon the skin or mucous membranes or which may influence the action of any ingredient. The source of animal and vegetable proteins utilized in parenteral products must be declared on the label.

The labels or labeling should also bear such information concerning any other components which are deemed essential for the safe and intelligent use of accepted products.

*Changes in Composition.*—Any alterations in the composition of an accepted product and the reasons for such change must be brought promptly to the attention of the Council.

**RULE 4.—Tests and Standards.**—*Suitable tests and standards must be submitted to establish the identity, purity, tolerances and potency of the active ingredients and of the finished product.*

*Errors in Manufacture or Labeling.*—A firm with an accepted product is held responsible for immediately notifying the Council of errors in compounding, sterilization or labeling which are discovered after release for distribution into commerce.

**RULE 5.—Nomenclature.**—*A trade name is acceptable for each brand of a drug, mixture of drugs or separately marketed vehicle if it is not therapeutically suggestive nor pre-empted by prior official status, and if the appropriate official or generic designation for the drug is distinctly displayed with it.*

*Definitions.*—For the purposes of this rule, the following definitions have been adopted.

*Brand Name.*—A “brand name” is the trade or protected name applied to a single drug, mixture of drugs or separately marketed vehicle as supplied by one firm. (For instance, in the case of a single drug, Artifel might be a brand name of a firm for its phenobarbital; in the case of a mixture, Sulozine might be a brand name for a firm’s combination of sulfadiazine and sulfamerazine; in the case of a topical vehicle, Olafene might be the brand name for one firm’s ointment base.) Brand names as applied to specific drugs or topical vehicles should not be confused with a general “brand mark” or trade symbol used to identify all the products of one firm nor with a “line name” used to designate a group of related drug preparations as supplied by a single firm. General brand marks or symbols, used to identify a firm rather than a specific product or type of products marketed by the firm, normally do not require consideration from the standpoint of nomenclature.

*Line Name.*—A line name is a trade name applied to a group or series of related pharmaceutical preparations having some common distinctive feature in addition to being products of the same firm (e.g., tabloid, hypoloid, magmoid, depo—).

*Generic Name.*—A generic name is an accepted name available for unrestricted use which is unprotected or for which trademark protection has been waived.

*Name for Official Article.*—A brand name for an official drug will be recognized only if such name actually was in public use



before the drug was first admitted in essentially the same form to the *U. S. Pharmacopeia* or *National Formulary*. The date of such inclusion is understood to be that of the first galley proof of the *U. S. Pharmacopeia* or of the Bulletin of the National Formulary Committee.

**Advantage of Generic Names.**—The interests of the patient and physician are best served by adoption of an abbreviated scientific name for general use in prescribing, naming and identifying agents with unwieldy chemical names. The Council believes that the use of generic names in the place of trade names for prescribing tends to diminish confusion and the difficulties in learning a multiplicity of names for the same drug. To encourage the use of the generic name, which is freely available to all, the Council requires the generic or official designation of a drug to be adequately displayed and not unduly subordinated to the brand name in labels, labeling and advertising.

### **Selection of Names**

**Generic Names.**—When practicable, generic names should be coined to conform to scientific usage as advocated by the American Chemical Society and American Society of Biological Chemists.

**Brand Names.**—Descriptive names are desirable, but purely fanciful names may be recognized if they are coined to avoid therapeutic suggestion, confusion with other names for the same or different substances and misleading connotations as to identity.

**Names of Salts and Esters.**—Brand or generic names for simple chemical salts and esters should be coined so as to apply only to the parent drug. (For instance, if the parent substance is given the brand name of Artificialine, and is basic in character, its salt would be designated as Artificialine Chloride; if acid in character, its salt would be designated as Sodium Artificialine or Artificialine Sodium.) Exceptions to this requirement may be permitted when, as judged on the merits of each case, at least one of the following circumstances prevails: (1) the compound significantly alters the action and therapeutic scope of the drug; (2) the usual chemical terminology is too lengthy or unwieldy for practical usage; (3) the introduction of other salts, esters or the free drug is impossible or highly improbable.

**Dosage Forms.**—Dosage forms of a drug should be identified so as to indicate the nature of the preparation by suitably descriptive terminology (for example, Elixir Artificialine Hydrochloride, Powder Artificialine Hydrochloride or Tablets Artificialine Hydrochloride). A brand or generic name is not eligible for application to only one dosage form of a drug if other dosage forms are marketed under another name by the same firm.

**Topical Vehicles.**—Brand and generic names for separately marketed ointment bases and other topical vehicles are eligible for recognition on the same basis as for single drugs or mixtures, providing such names are not also applied to dosage forms of drugs in which the vehicle is employed. The use of special names for vehicles in designations of drug preparations is likely to



multiply confusion in the terminology essential to identify the drug component. Therefore, names for vehicles should be devised to suggest the type of base rather than any particular component.

**Mixtures.**—Generic and brand names for mixtures containing two or more active ingredients should be coined from the chief components. When one or more of these are present as a salt or ester, they need not comply with the above requirement applied to single agents for distinctive designation of such derivatives.

**Subordinate Components.**—Components of secondary importance which in some degree modify the therapeutic action of the mixture are preferably named without abbreviation (e.g., Solution Procaine Hydrochloride with Epinephrine 1:100,000). Preparations containing 1 per cent or more of benzyl alcohol or more than 0.5 per cent chlorobutanol must include these ingredients as part of the name.

**Use of Numerals and Letters.**—The use of numerals or lettered abbreviations or both in whole or part as generic or brand names is considered objectionable except upon adequate scientific justification. Numerals or letters utilized on labels for coding or catalogue identification should be separated clearly from the names of the products.

**Names of Biologic Products.**—Therapeutically suggestive names are not considered objectionable for serums, vaccines, antitoxins and similar articles.

**RULE 6.—Patents and Trademarks.**—*The name, number and date of any domestic or foreign patents or trademarks pertaining to an article must be furnished to the Council.*

**RULE 7.—Advertising.**—*Claims for products shall be limited to those recognized for inclusion in New and Nonofficial Remedies.*

**Definition.**—For the purpose of this rule, "advertising" is broadly defined to include any and all promotional methods used in the distribution and sale of a product. It therefore comprises labels, labeling, mailings and all printed matter; graphic, written or spoken communications including projected pictures, radio, television and other exhibits which pertain to the article. The term, "labeling," is interpreted to mean material which physically accompanies the package in which an article is marketed. Advertising may be separated into two general classes, (1) advertising to the medical and allied professions and (2) advertising to the public.

**Responsibility of Firm.**—The Council does not undertake to police or censor the advertising of accepted, exempted or re-accepted products, but places upon the firm the responsibility for making only authorized claims. Claims which are disallowed as a condition of acceptance after consideration of all evidence and statements submitted must be abandoned or appropriately revised before the acceptance is an accomplished fact.

**Submission of Advertising.**—All current and new advertising for submitted, accepted or exempted products should be presented for the information of the Council. The Council cannot edit advertising copy word for word, but rather indicates the general type of revision which may be required. Whenever doubt exists as to re-

wording or rephrasing, the advice of the Council should be sought in advance of printing or distribution.

**References to Medical Literature.**—References may be used in advertising to published or unpublished reports by permission of the author, provided the name of the investigator, source and date of publication are indicated. Removal from original context of brief quotations to focus attention upon phrases or statements which do not fairly reflect the authors' ultimate conclusions is considered misleading, as well as advertising which contains abstracts of only favorable reports for the product when contrary evidence is also available.

**References to New and Nonofficial Remedies.**—Direct quotations, facsimile reproduction, abstracting or translating into a foreign language of any portion of *New and Nonofficial Remedies* is subject to authorization by the Secretary of the Council.

**Seal of Acceptance.**—The Council permits the use of its official Seal of Acceptance on packages and in advertising only for those products accepted for inclusion in *New and Nonofficial Remedies*. The display of the Seal should not be employed in a manner which might pervert its meaning or detract from its dignity. The size of the Seal on packages and in advertising should be in proportion to the dimensions of the advertisement only to permit ready recognition. The following statement concerning its significance may be used in connection with the Seal: "The 'accepted' Seal denotes that (name of article) has been accepted for *New and Nonofficial Remedies* by the Council on Pharmacy and Chemistry of the American Medical Association."

Variations in the phraseology cited in regard to the Seal must be submitted to the Council and found acceptable before they may be used. When, for any reason, acceptance of an article is rescinded, the Seal must not appear on new labels or advertising; old labels and advertising featuring the Seal must not be in circulation or before the public longer than 6 months subsequent to notification of the revocation. The Seal of Acceptance shall not be used in the promotion of exempt articles; however, exempt drugs may use the designation N.N.R. in advertising.

**Advertising of Exempt Drugs.**—Claims for an exempt product shall not exceed those recognized in the last edition of *New and Nonofficial Remedies* in which the product was described. Exempt products are eligible for advertising in the publications of the American Medical Association, without the seal of acceptance.

**Foreign Distribution.**—When acceptance of an article for inclusion in *New and Nonofficial Remedies* is declared in the advertising distributed to foreign countries, advertising claims shall be limited to those recognized for inclusion in *New and Nonofficial Remedies*.

**Experimental Uses.**—Claims for experimental uses for an accepted product are not permissible on labels, labeling or ordinary advertising. If a firm wishes to issue an informative review of the literature elaborating on all phases of use of an accepted product, experimental uses may be included by presenting an unbiased



abstract with appropriate references to all pertinent favorable and unfavorable scientific literature, but without promotional statements, references to Council acceptance, or use of the Seal of Acceptance. Booklets or brochures ordinarily employed for promotional purposes must exclude unestablished information.

**Advertising of Unaccepted with Accepted Products.**—Accepted or exempt products should not be used for promotion of the sale of unaccepted products. Distribution of separate advertising pieces for accepted and unaccepted products in the same envelope is permissible only when the Seal of Acceptance or a reference to *New and Nonofficial Remedies* is clearly affixed to those enclosures which pertain to accepted products. This requirement does not apply to price lists and catalogs where, at the discretion of the firm, accepted status of a product may be indicated by the Seal of Acceptance or the designation N.N.R.

**Superlative Claims.**—Sound therapeutics require avoidance of overenthusiastic claims and inferences for a product as well as avoidance of disparaging statements of **recognized standards** or competing products. Proper definition, qualification and avoidance of sweeping statements are essential in the preparation of suitable advertising. The use of the personal signature of a physician or the facsimile of such a signature is generally considered objectionable because it may create an exaggerated or misleading impression of value.

**Claims for Safety.**—Unqualified statements that a product is nontoxic or nonirritating ignore the possibility of varying circumstances which may be encountered in its use. The firm is held responsible for proper qualification of claims so that physicians are not misled in regard to safety.

**Permanently Affixed Names.**—It is considered desirable to permit physicians to prescribe anonymously when knowledge of the remedy may be detrimental to the patient. Any permanently affixed names or other devices for identifying the article to the public will not be accepted if the Council believes that it would be likely to lead to serious abuse.

**Advertising to the Public.**—Certain limited classes of products, which in the judgment of the Council may be used with reasonable safety by the public for the palliation of certain symptoms or prevention of infection, are acceptable for inclusion in *New and Nonofficial Remedies*. These include (a) topical disinfectants, antiseptics, fungicidal agents and pediculicides; (b) laxatives; (c) antacids; (d) nonhabituating analgesics; (e) nasal decongestant inhalers. In each case the Council believes it is essential to weigh carefully the potential danger that can result from self-medication and to determine whether the product concerned can be safely employed by the public.

## Presentation of Articles

Each presentation should be addressed to the Secretary, Council on Pharmacy and Chemistry, American Medical Association, 535

N. Dearborn Street, Chicago 10, Illinois. All letters concerning submitted products should be forwarded in duplicate.

The procedures to be followed in the submission of (1) new articles or brands, (2) new dosage forms of already accepted articles and (3) new firms are outlined below.

### **New Article or Brand**

A. Description (See outline below): **3 copies.**

B. Evidence (laboratory and clinical, see discussion below): Required only of new articles, except when a new brand involves claims for use, administration or dosage not recognized in *New and Nonofficial Remedies*:

1. Reprints or photostats of complete reports: **2 copies.**

2. Unbiased abstract reviewing all data and giving references or sources of information: **22 copies.**

C. Labels (container, package, carton) for each submitted dosage form and size, mounted on letter-size paper: **22 separate sets.**

D. Package circular or other enclosures and all proposed or currently distributed promotional literature for all submitted dosages: **22 copies.**

E. Trade package specimens of the smallest quantity marketed

1. Injectable and other sterile preparations, biologics, antibiotics, topical anti-infectives and disinfectants: **6 of each dosage form and size.**

2. All other products: **3 of each dosage form and size.**

F. Bulk sample of the active ingredient as used in manufacture: 10 Gm. for a new article. If a new brand or a new article is rare or expensive, a lesser amount sufficient to permit duplicate chemical tests for identity, purity and assay may be submitted. When the finished article is supplied in pure, unmixed or undiluted form: **A sufficient number of additional trade package specimens to provide an equivalent amount.**

Bulk samples of one or more of the components of separately marketed topical vehicles need not accompany a presentation for this type of product. When necessary for analysis of such articles, specified bulk samples of the components will be requested.

### **Additional Dosage Form or Size**

A. Description (See outline below) covering completely only items 1, 2 and 3, and the portions of other items (including all essential chemical or microbiologic information) pertinent to the formulation or size submitted: **3 copies.**

B. Evidence: Only when a new use, different route of administration or wider range of dosage is proposed: **As for a new article.**

C. Labels: **As for a new article.**

D. Circulars and advertising whenever these are new or revised beyond mere listing of the additional dosages: **As for a new article.**

E. Specimens: **As for a new article.**

F. Sample of active ingredient only if a period of two years or more has elapsed since submission of the first dosage form of the article: **As for a new article.**



**New Firm.**—When a firm makes its first presentation, this should be accompanied by:

A. A statement, as outlined below, dated and signed by a responsible officer of the company: **2 copies.**

1. General policies, scientific aims and methods of marketing.

2. Names and qualifications of laboratory and control personnel.

3. Agreement to abide by the rules and subsequent requirements of the Council as these apply to any product which may be accepted for *New and Nonofficial Remedies*, and to notify the Council of any change in composition, market status or error in manufacture which may occur with products subsequently accepted.

B. The catalog, price list or typewritten equivalent covering all products marketed for human medicinal use: **22 copies of each.**

## Experimental and Clinical Evidence

All pertinent animal or other experimental laboratory studies and all clinical reports on the use of the agent should be submitted, including both favorable and unfavorable results and the incidence of dangerous or fatal reactions. In the case of new drugs, the evidence should cover absorption, action, toxicity and fate or excretion. For new disinfectants, contraceptive agents, mixtures of drugs and enteric-coated preparations, evidence should be presented also to meet the special requirements listed in the section on criteria for the evaluation of certain products. Additional dosage forms for which a use, route or dosage is recommended which differs from those previously accepted should be accompanied, like new articles, by evidence to substantiate the new claims. Whenever evidence is required the pertinent information should be summarized briefly under this heading and a notation made of the detailed reports and abstracts to be separately submitted.

## Outline of Description

Each description should be supplied in triplicate, typewritten or printed on letter-size paper bearing the name of the firm, the date forwarded and signed by the person to whom subsequent correspondence should be addressed. Different salts and esters of the same drug should be presented separately, but all dosage forms which contain the same active component should be described together to avoid unnecessary repetition. For each chemical compound presented, the following items should be tabulated and discussed in the order specified:

1. **Brand and Generic Names of Active Ingredient(s).**—Both brand and generic names, when a trade name is used, the official or Council-adopted generic designation being given after the protected name. When the article is official, name of the compendium U.S.P., or N.F., in which it appears and the date when the trade name was first used publicly to designate the article. Trade names for official

drugs are acceptable only if they were used prior to their admission to either of the official compendia. When the article is not official and no generic name has been adopted by the Council, a scientifically derived generic designation should be proposed for consideration. This name is to be displayed with the trade name on the labeling.

2. *Dosage Forms and Sizes Submitted*.—A list by appropriate designations of all formulations, concentrations and sizes of the article for which consideration is desired. When additional forms, concentrations or sizes of a previously accepted brand of an article are submitted, only those not previously considered should be listed. See the N.N.R. monographs concerned and the section on general provisions and labeling requirements for limitations in dosage sizes of certain drugs.

3. *Composition of Each Formulation*.—The per cent or weight per dosage unit and the purpose of *all* constituents (active and inactive) for each formulation and dosage specified above. Inactive as well as active components should be identified by official or generic designations whenever applicable. The percentage of each ingredient of enteric or other coating employed to delay disintegration of solid dosage forms should be revealed when products of this type are involved. For chemical contraceptives which contain a perfume, a quantitative statement of all its ingredients is also required.

4. *Indications or Uses*.—Enumeration of claims for actions and uses of all submitted forms as proposed or as currently expressed in advertising for the article. Contraindications and limitations of use as well as advantages should be listed. This requirement does not apply to additional brands, dosage forms and sizes which do not involve new claims. In such instances a reference to the appropriate *New and Nonofficial Remedies* monograph is sufficient.

5. *Dosage and Administration*.—Dosage and method of administration for each dosage form submitted and for each condition of use. Whenever possible, the initial, average and maximum amounts per time interval should be indicated for adults and, when recommended, for children or infants. When pertinent, the amount of the preparation ordinarily required to produce and maintain effective blood or tissue concentration should be stated in terms of body weight for both adults and children. Warning concerning possible side effects or cumulative action in relation to total dosage and duration of administration should be included here. This requirement does not apply to additional dosage forms that do not involve a new route or amended dosage schedule.

6. *Patents and Trademarks*.—Country of origin, number and date assigned and expiration date, of all registered U. S. and foreign patents and trademarks which are applicable to the submitted article. When these are pending, that fact should be stated; the number later assigned in the case of U. S. registration also should be transmitted.

7. *Chemical Data*.—Chemical data whenever applicable to cover the following points:

(a) *General Information*.—Chemical name, empirical and struc-



tural formulas and molecular weights of each active ingredient, the name of the supplier or suppliers and a sample of each active ingredient. Where the term "active ingredient" is not strictly applicable, only chemical information is required and should be stated for all components.

If the substance is new, references to the chemical literature, especially that containing proof of the structure.

(b) *Physical Properties*.—Data on appearance, taste, odor, melting point, boiling point, stability (to moist and dry air, heat, light and on storage), refractive index, specific gravity, solubilities at 25°, important incompatibilities, pH of a solution (preferably that of the concentration of the liquid dosage form), optical density, optical rotation, crystallographic constants, viscosity and refractive indexes, whenever these data are applicable to the active ingredient.

Physical properties stated must be those of the grade of ingredient actually used in the manufacture of dosage forms and not properties of highly purified laboratory samples.

(c) *Identity Tests*.—Detailed directions for tests to identify the active ingredients and distinguish them from chemically or therapeutically related materials.

The tests should always confirm the presence of the important active groups. Specific tests for individual molecules are desirable. At least one test should be described using some easily measured property, such as melting point, which will indicate a clear chemical distinction between a derivative and its parent compound.

(d) *Purity Tests*.—Tests for the detection of impurities which may have been present in the active ingredient originally or as a result of the method of manufacture, e.g., the volatile matter and ash. In the determination of volatile matter, the method, desiccant and minimum time of drying should be stated. The temperature employed should be one of those selected by the National Formulary Committee as standard (*Bull. Natl. For. Comm.* 16:155 (1948): 60, 80, 105, 120 or 150°).

(e) *Assay*.—Protocols of bio-assay when pertinent should be stated in addition to the following appropriate chemical information.

(1) *Active Ingredient*. Complete instructions or appropriate references to published methods containing complete instructions for the procedure for assay of each active ingredient. Spectrophotometric methods are preferable to titrimetric methods and these in turn to gravimetric methods. Where special apparatus is required for an assay, an alternative method employing equipment available to most laboratories should also be submitted.

(2) *Dosage Form*. Detailed directions for the detection, separation and assay of active ingredients in all dosage forms. The method of assay for dosage forms should be that used for the active ingredient wherever possible.

The accuracy and precision of the methods and the limits of purity which the manufacturer considers satisfactory should be stated.

(f) *Tolerances*.—The limits of concentration of the active ingredient, tolerances for the fill of ampuls and bottles, weight of

capsules, suppositories, tablets or any dosage forms considered to be acceptable by the manufacturer. Where limits and tolerances exceed those for comparable products given in the official compendia or N.N.R., reasons for the difference should be stated.

**8. Microbiologic Data.**—Detailed microbiologic information is required for all injectable preparations, biologics, antibiotics, topical anti-infectives and disinfectants. The following points should be covered as they apply to any of these classes of agents:

(a) Bacteriologic and biologic assays with protocols for identity, strength, quality and purity.

(b) Sterilization procedures.

(c) Sterility tests.

(d) Removal of pyrogens.

(e) Pyrogen tests.

(f) Toxicity tests.

(g) Determination (in vitro and in vivo) of spectrum affected by antibacterial, antifungal, antiviral and antirickettsial properties of the active ingredient(s) and of any other antimicrobial ingredient present. See also the section on criteria for the evaluation of certain products for further requirements for topical anti-infectives and disinfectants.

**9. Preparation and Control Procedures.**

(a) General description of method of manufacture. State methods for both active ingredient(s) and dosage forms submitted. Details must be sufficient for the Council to assure itself that the process will result in a product of the claimed identity, strength, quality and purity.

(b) Control procedures. Except for products certified by the U. S. Food and Drug Administration, the following points concerning control procedures should be indicated for each dosage form submitted; when these are the same as for previously submitted products that fact should be stated, and when only part of the procedure is the same the points of departure should be covered:

(1) Precautions to insure proper identity, strength and purity of the raw materials.

(2) Precautions to preserve sanitary conditions in space allotted to storage of raw materials.

(3) Use of serial numbers to identify each lot of raw materials and the use made of such numbers in subsequent plant operations.

(4) Method of preparation of formula card and manner in which it is used. Specimen blanks of the forms used should be supplied in duplicate.

(5) Manner in which weights and measures of each ingredient are checked when formula is being prepared.

(6) Determination of total weight or volume of each batch at any stage of the manufacturing process subsequent to making up a batch according to the formula card and at what stage and by whom this is done.

(7) Methods of maintaining sanitary conditions within the manufacturing plant and avoiding contamination of the drugs with filth, dust and extraneous material.



(8) Check of the total number of finished packages produced from a batch of the drug with the theoretical yield.

(9) Precautions to insure that the proper labels are placed on the drug for a particular lot.

(10) The analytic controls used during the various stages of the manufacturing, processing and packaging of the drug, including a detailed description of the collection of samples and the analytic procedures to which they are submitted. If the article is one which is represented as sterile, the same information should be given for sterility controls.

(11) An explanation of the exact significance of control numbers used in the manufacture, processing and packaging of the drug, including any code numbers which may appear on the label of the finished article.

(12) Additional procedures designed to prevent contamination and otherwise insure proper control of the product.

(13) Examination of representative samples of each lot of the drug by another laboratory (government or private) prior to distribution. Name of this laboratory.

*Note.*—When any of the procedures described under the headings chemical data, microbiologic data, preparation and control procedures are the methods (unmodified) required or recommended by Federal Law, the U.S.P., N.F., National Institutes of Health, Association of Agricultural Chemists, *New and Nonofficial Remedies* or stated in scientific journals, specific references to such sources may be substituted for the detailed description of these technical procedures.

## CRITERIA FOR THE EVALUATION OF CERTAIN PRODUCTS

Certain groups of products present problems that can best be solved when uniform consistency is maintained in the collection of evidence for the preparations in these groups. Accordingly, the Council from time to time proposes criteria to serve as guides in the planning of experiments and the examination of results intended to obtain data to meet the Council rules. So far the Council has prepared criteria for anti-infective agents, antifungal agents, contraceptive agents, enteric-coated products, mixtures and topical vehicles.

**ANTI-INFECTIVES.**—For new products (i.e. not in N. N. R.) involving claims of antiseptic, bacteriostatic or germicidal effectiveness, or when new claims are advanced, protocols of bacteriologic examination signed by a reputable bacteriologist, and evidence of clinical usefulness which will present studies on toxicity, pharmacology, etc., should be submitted. Where published papers are available, references should be cited.

Criteria for evaluation of skin disinfectants which the Council deems advisable include:

### (A) For Antibacterial Agents

1. Phenol coefficients or other *in vitro* tests in the absence and

in the presence of serum, using both vegetative bacterial cells and clostridial spores, with suitable recovery mediums containing, if known, neutralizing substances for the disinfectant being tested.

2. Data on germicidal efficiency under conditions simulating actual use by the method of Price (Price, P. B.: the Bacteriology of Normal Skin: A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleaning, *J. Infect. Dis.* 63:301 [Nov., Dec.] 1938; Ethyl Alcohol as a Germicide, *Arch. Surg.* 38:528 [March] 1939) or, better still, by an extension of the method of Price (Bernstein, L. H. T.: Standardization of Skin Disinfectants, *J. Bacteriol.* 43:50 [Jan.] 1942). The complications due to possible effects of the germicide on the skin itself should be taken into consideration (Cromwell, H. W., and Leffler, Ruth: Evaluation of "Skin Degerming" Agents by a Modification of the Price Method, *ibid.*, p. 51).

3. Data on germicidal efficiency by an animal method, such for example as suggested by Alice H. Kempf and W. J. Nungester (An In Vivo Test for the Evaluation of Skin Disinfectants, *ibid.*, p. 49) or R. W. Sarber (*ibid.*, p. 50).

4. Evidence from animal experiments regarding irritant action on skin and mucosae and regarding systemic toxicity.

5. Critical clinical evidence supporting claims of harmlessness and efficacy.

6. Data on the bacteriostatic activity as distinguished from the germicidal activity of the disinfectant.

**(8) For Antifungal Agents.**—An extensive discussion of this subject appears in *The Journal* as a Council report (July 14, 1945, vol. 128, pp. 805-811). For guidance the data suggested may be divided into three parts: (1) laboratory tests of the fungicide, (2) clinical tests and (3) toxicity tests, and obtained as follows:

**1. In Vitro Tests of Fungicide.**—The phenol coefficient test for disinfectants and antiseptics as modified by the American Public Health Association subcommittee should be used. For convenience, this is resubmitted, but in synoptic form. A detailed report is published in the *American Journal of Public Health* for 1945 of the Standard Methods Committee for the Examination of Germicides and Antibacterial Agents.

(a) The test fungus should be *Trichophyton interdigitale*. A suitable strain, No. 9533, is procurable from the American Type Culture Collection, Georgetown University, 3900 Reservoir Road, Washington, D. C. It should survive 10 minutes' exposure at 20° to phenol 1:60 but not to a strength of 1:45.

(b) Spore suspensions of this test fungus should be prepared from ten-day agar cultures in a concentration of 5 million conidia per cubic centimeter. For performing the test, 0.5 cc. of this suspension is added to 5 cc. of the fungicide concentration being tested.

(c) Samples for viability tests should be taken at intervals of 5, 10 and 15 minutes and planted in a liquid medium containing 1 per cent Difco Neopeptone and 2 per cent chemically pure dextrose, pH 5.6-5.8. A liquid medium is essential for the rapid



dissipation of the fungicide carried over. In the case of fungicides exerting a strong fungistatic effect, subcultures must be made.

(d) The so-called "*Trichophyton rosaceum*" should not be used as a test species. It is less resistant than *Trichophyton* when tested by the method outlined here, although it often appears to be more resistant in plate tests.

The test procedures follow the plan outlined in United States Department of Agriculture Circular 198 for the determination of phenol coefficients.

**2. Clinical Tests and Their Evaluation.**—This involves the use of prepared preliminary outlines and of a protocol for each patient.

(a) Selection and Grading of Patients: The number of patients should be sufficiently large to permit their division into a test group and a control group. Each of these, in turn, should be large enough to permit results that will be significant when later divided into subgroups for purposes of analysis. In consultation, a group of dermatologists has estimated 50 as the minimum number for both the test and the control group. Bed patients are not suitable, because dermatophytosis sometimes disappears spontaneously with bed rest.

Each of the two groups should contain an equitable representation of mild, moderate and severe cases. It is advantageous to indicate on a diagram on the protocol just what the extent and type of lesion are for each patient.

(b) The Environment: This and other circumstances should be comparable in the two groups. The groups should be tested simultaneously. Thus, results from group A which were secured in winter would not be comparable to ones secured on group B in the summer; dermatophytosis is worse in the summer. Similarly, results should be checked with age groupings in the two test groups lest it have too much of a disturbing influence in the evaluations. Young people are far more predisposed than the aged.

(c) Laboratory Diagnosis: As a check against the clinical diagnosis, scrapings should be examined under the microscope for the presence of fungus and also cultured at the beginning of the studies. These examinations should be regarded as only supplementary to the clinical findings; many cases of valid dermatophytosis fail to yield confirmatory laboratory evidence, but the laboratory examinations may clarify doubtful clinical cases, and a knowledge of the identity of the species may be valuable when analyzing therapeutic results later. Thus, a fungicide might be eventually discovered which was efficacious against *Trichophyton purpureum* or other fungus but not against other species, and vice versa.

(d) Number and Duration of Treatments: As a working rule, applications should be made at night and in the morning for 2 weeks. A final or subfinal examination should be made at the end of 4 weeks.

(e) Faithfulness of Patient to Treatment: The investigator should appraise the human type of each patient before admitting him to the test series and have no hesitance in rejecting the unpromising ones. Lapses in treatment demand that the patient be removed from the series and is one more reason for securing a



larger number of patients at the beginning of the work than will be employed in the final evaluation.

(f) **Privacy on Part of Patients:** Patients should be requested not to discuss their treatment programs with other patients; they may influence one another's opinions. For obvious reasons, clinical tests should not be conducted on patients who are employed in plants which have a gainful interest in the fungicide being tested.

(g) **Local Irritant Effect of Fungicide:** This should be substantially nil, considering the number of fairly effective therapeutic agents now existent which are free from irritant effects. Certainly, the development of any reactions that are at all severe should at once condemn the agent.

(h) **Sensitization to the Fungicide:** This factor enters into and is routinely inquired for in tests of local applications in general. In the case of dermatophytosis it will largely take care of itself during the clinical tests of fungicidal value, where the applications are "interrupted" in the natural course of events. The appearance of flare-ups shortly after the eighth day of treatment should be watched for. If they do appear, a special set of tests for sensitization must be made.

(i) **Toxic Systemic Effects:** These should not play a role of importance in the treatment of dermatophytosis. Animal tests should be required save in exceptional circumstances, indicating whether the substance is toxic when administered internally and, if so, the amount that can be absorbed from skin. Such animal tests can follow the plans already developed for bacterial disinfectants and antiseptics. The Bureau of Ships Circular 51D6 (Int.), Dec. 15, 1942, page 4, paragraph F.-2d may be followed in this connection.

(j) **Readings of Results of Treatment:** These should be made without any knowledge of the identity of the patient or of the treatment that has been employed; an assistant should have removed, if possible, any traces of telltale fungicide that may remain. Only in this way can the factor of bias be completely removed and a fair, impartial evaluation secured. If at all possible, the readings should be made by a disinterested person.

(k) **Mycologic Checks on Therapeutic Results:** These will have value only of a kind supplementary to the clinical opinions because of the increased difficulty in laboratory demonstration of fungi in treated lesions. At the conclusion of therapy they should be made on the "cured" and "nearly cured" patients and again on the cured patients 4 weeks after cure. Positive results will have larger definitive value because they will indicate that the fungicide has not killed. With negative results there is a possibility that fungi are still present but not demonstrable. In any event this mycologic check should be performed so that the data may be available when making final evaluation. The competence of the examiner in recognition of fungi is of paramount importance.

(l) **Grading of Results:** "Cured," "almost cured," "improved," "stationary" and "worse" are suggested, but each worker is at liberty to select any system that suits his purposes; but he should be clear beforehand for his own guidance as to the criteria for grading; from this there should be no deviation later. A subdivision

like this into five grades reduces the number of cases available for subsequent statistical purposes and illustrates once again the necessity for numerous patients to begin with. Opinions of patients as to results should not be depended on too much; in cases of doubt they should be discounted. Patients commonly regard themselves as cured when itching ceases. It will be conducive to accuracy if the physician has an assistant who will independently grade the results, the final grading being decided in consultation on the spot.

**3. Toxicity Tests.**—These should be performed depending on the individual circumstances surrounding the chemical concerned. Where there is a hazard the Bureau of Ships circular entitled "Disinfectant, Germicide and Fungicide," page 4, paragraph F.-2d may be followed. Ten healthy adult albino rats weighing between 150 and 250 Gm. should be employed, none pregnant. They should be fed as usual. Three-tenths cc. of the fungicide (standard strength) per kilogram of body weight should be slowly inserted obliquely into the peritoneal cavity. The animal should then be given the usual food and water and observed for untoward effects for 72 hours.

**CHEMICAL CONTRACEPTIVE AGENTS.**—For guidance in reviewing contraceptive products, the Council on Pharmacy and Chemistry has proposed the following criteria:

1. The use of the word "contraceptive" need not be limited to materials which will prevent conception on every occasion of use.
2. Evidence shall be furnished that use of the material decreases the incidence of pregnancy. This evidence may be secured in connection with occlusive devices unless the manufacturer's advertising is directed chiefly toward the use of the jelly or cream without such devices. It is desirable that each case reported should be observed for at least 12 months, and that the minimum of 75 patient-years of experience should be reported. (Thus 50 patients for 18 months or 25 patients each followed for 3 years would be the equivalent of 75 patients for 12 months.) If cases are excluded from the series on the basis of their being irregular users, the number excluded and the nature of the evidence justifying their exclusion should be stated.
3. Evidence shall be submitted that 100 or more couples have used the material on six or more occasions without irritation or injury.
4. Evidence is desirable that 12 or more women have received vaginal applications of the recommended dosage on 21 successive days without subjective irritation or injury and without evidence of physical damage shown on speculum examination by a physician with special experience in this field. Thus, inspection of the vagina at least once a week should be done as a protection to the patient in case the jelly proves to be irritating.
5. The quantitative formula from which the contraceptive mixture is prepared shall seem to the Advisory Committee to be safe and, presumably, effective.
6. The consistency shall be satisfactory to the committee. It shall



not show separation into more liquid and more solid portions visible to the naked eye.

7. Evidence shall be submitted that the consistency is not substantially changed after storage for 12 months at 27°.

8. The consistency shall be reasonably uniform from batch to batch.

9. The spermicidal time of the contraceptive material as measured by the method of Brown and Gamble (*J.A.M.A.* 148:50 [Jan. 5] 1952) with proportions of material, isotonic solution of sodium chloride and semen of 1:4:5 shall be 30 minutes or less as measured by the average of four or more tests.

10. The use of jellies or creams suggested by the manufacturer need not be limited to use in conjunction with an occlusive device.

11. If a syringe applicator or nozzle is furnished for use in connection with the jelly or cream, it shall be sufficiently translucent to permit the detection of air which might lead to inadequate dosage.

12. If a perfume is used, a quantitative statement of ingredients is required.

**ENTERIC-COATED PREPARATIONS.**—In general, enteric coating for a drug is considered justifiable only when (1) the absorption or action of the active ingredient should be restricted to the intestinal tract or should be retarded by fractional coating to prolong its effect, (2) the active ingredient is irritating to the gastric mucosa or causes nausea on release within the stomach or (3) the active ingredient is inactivated by the gastric juice. Drugs submitted in the enteric-coated form should be accompanied by evidence satisfying one or more of these requirements, together with data which demonstrate that the coating employed successfully accomplishes release of the active ingredient within the intestine. The percentage of ingredients in the enteric coating must be stated along with that of all other ingredients of such dosage forms.

The Council does not consider enteric-coated dosage forms of such drugs as diethylstilbestrol or digitalis acceptable because they do not meet the above requirements and are not superior in any way to plain dosage forms.

**MIXTURES.**—The effects of drugs are intrinsically so complex that it is generally advisable to administer them singly. However, concomitant administration of two or more medicinal agents may be indicated if the particular drugs assist each other to produce an effect that no one of them could effect alone, or if this procedure significantly reduces toxic or side effects. It is ordinarily wiser to administer them separately in order that the dosage and frequency of administration of the individual drugs may be varied in accordance with the patient's requirements.

There may be advantages in prescribing mixtures "ready-made" when the administration of the components in the same fixed ratio can be justified, as with certain vitamin preparations; when they are always given at the same time, as with procaine hydrochloride



and epinephrine injections; and when extemporaneous compounding is too complicated.

The Council therefore accepts mixtures only if they fulfill the following conditions:

1. (a) The active ingredients together accomplish significant therapeutic results that could not be expected from one ingredient alone, and/or

(b) Use of the ingredients together diminishes the toxic or side actions.

2. The particular ratio of the active ingredients can be justified so as to avoid unnecessary multiplication of ratios for practically equivalent mixtures.

3. The ingredients cannot conveniently be compounded extemporaneously.

**TOPICAL VEHICLES.**—Vehicles, such as ointment bases, which are considered suitable for the incorporation of topical medication, are eligible for inclusion in *New and Nonofficial Remedies*, providing such vehicles are separately marketed for compounding prescriptions and/or for manufacturing use and they meet the requirements as specified under criteria for the evaluation of certain products. When such products are sold for manufacturing use only, they are not eligible for inclusion or retention in *New and Nonofficial Remedies* after the formula is admitted to either the *U. S. Pharmacopeia* or the *National Formulary*.

## GENERAL PROVISIONS AND LABELING REQUIREMENTS

### Protein and Amino Acid Preparations

Thus far, the Council considers as acceptable for nutritional purposes only those mixtures that provide adequate amounts of each of the essential amino acids. For the present, and until more evidence becomes available, the Council restricts acceptance of such amino acid mixtures for either oral or intravenous administration to hydrolysates of suitable pure proteins (such as casein) or good sources of protein (such as blood) in which more than 50 per cent of the total nitrogen present is in the form of alpha amino nitrogen. This minimum degree of hydrolysis is essential to justify the designation of such products as hydrolysates and to insure the non-antigenic properties. The Council requires that evidence of non-antigenicity be submitted with each product. The Council has permitted the addition of carbohydrate to such hydrolysates in proportions suitable for injection. The Council has not, as yet, accepted preparations containing added vitamins or other substances considered essential for adequate nutrition pending adequate justification for such preparations.

Hydrolysates of pure proteins, such as casein, lactalbumin and fibrin, are properly described as "protein hydrolysates." They may be designated as "Casein (Lactalbumin, Fibrin) Hydroly-

sate." Hydrolysates of good sources of protein such as blood, liver and yeast are distinguished from pure protein hydrolysates and will be individually described under separate generic designations appropriate to indicate their respective derivation, e.g., Blood (Liver, Yeast) Hydrolysate. Restoration or addition of amino acids to hydrolysates should be limited to those considered "essential" for human nutrition and should be sufficient to furnish the equivalent of the biologically active form in an amount proportionate to the original source, or sufficient to meet actual requirements if the quantity needed is known. Products to which one or more amino acids have been restored or added or in which one or more of them have been at least partially removed should be designated as "Modified Casein (Liver, etc.) Hydrolysate." When carbohydrate such as dextrose has been added, the designation of such preparations should be expanded to indicate the carbohydrate component, e.g., "(Modified) Casein Hydrolysate with Dextrose ( ) per cent." When such products are supplied in the form of solution for intravenous injection, the designation should be prefixed by the word "Solution" and include the per cent of hydrolysate provided, e.g., "Solution Casein Hydrolysate 5 per cent (with Dextrose 5 per cent)." Such designations do not preclude, but should be adequately displayed with, acceptable trademark names. The Council requires that all hydrolysates be labeled with the appropriate generic designation (to include dextrose or other suitable carbohydrate when this is added), the identity of the protein or source of protein from which they are derived when this is not declared in the descriptive designation, the method of hydrolysis (acid, enzymatic or other), the nature of modification in amino acid content after hydrolysis (if any), the percentage of each amino acid or its equivalent that is present, and the percentage of alpha amino nitrogen that is represented in relation to the total nitrogen content of the mixture. Hydrolysates for parenteral injection should also be labeled to declare the sodium and potassium content. Council consideration of hydrolysates for acceptance is further predicated on adequate rat growth studies to demonstrate nutritive value and in the case of intravenous products, also on adequate clinical evidence to demonstrate freedom from antigenic, pyrogenic and toxic properties. Claims for special therapeutic purposes of hydrolysates other than for general protein deficiencies must be supported by specific scientific evidence.

Pure synthetic mixtures of amino acids for nutritional states or preparations of the individual pure amino acids used for specific therapeutic purposes will be given consideration as evidence for their usefulness is established. Preparations of intact proteins used orally as food supplements are considered to be outside the purview of the Council unless specific therapeutic value is established for such products.

## Vitamins

*Statement of Vitamin Potency.*—Vitamin A and vitamin D potency must be expressed in U.S.P. units. The vitamin content of



preparations of ascorbic acid, thiamine, riboflavin, nicotinic acid, nicotinamide, pyridoxine, menadione and similar vitamin K preparations must be expressed in milligrams and not in micrograms, gammas, or units.

Labels of vitamin preparations which supply in the recommended daily intake not more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food, Drug and Cosmetic Act, must show the proportion of the minimum daily requirements supplied in the recommended daily intake.

Vitamin preparations which supply in each unit (tablet, capsule, etc.) or in the recommended daily intake more than three times the minimum daily requirements set forth in regulations under Section 403 (j) of the Food, Drug and Cosmetic Act will be accepted if they are advertised only to the physician. To meet the requirements of the Food, Drug and Cosmetic Act with respect to adequate directions for use, such preparations must bear the statement "... daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of ... deficiency," or a more detailed statement of directions for use.

The above labeling requirements are exemplified in the following outline of statements which should appear on the main panel of the label:

*Restriction of Dosage Sizes.*—Consideration of dosage sizes of certain vitamins will be limited to the following:

Ascorbic Acid: Tablets: 10, 25, 50 and 100 mg. per tablet.

Menadione: 1 and 2 mg. per tablet; 1 and 2 mg. per capsule; 1 and 2 mg. per cubic centimeter in solution.

Nicotinamide: 25, 50 and 100 mg. per tablet; 25, 50 and 100 mg. per cubic centimeter in solution.

Nicotinic Acid: 25, 50 and 100 mg. per tablet. Solutions are not eligible.

Riboflavin: 1, 2, 5 and 10 mg. per tablet; 0.2 mg. per cubic centimeter in solution. (Higher concentrations are eligible.)

Thiamine Hydrochloride: 0.5, 1, 3, 5 and 10 mg. per tablet; 1, 5 and 10 mg. per cubic centimeter. No dosage form in a container larger than 10 cc. will be considered.

Vitamin A: 25,000 U.S.P. units or less per capsule, tablet or average dose of fluid.

#### Vitamin B Complex preparations:

1. Mixtures of pure thiamine, riboflavin and nicotinic acid providing in the recommended daily intake: 1 mg. thiamine, 1.5 to 2 mg. riboflavin, 10 mg. nicotinic acid or simple multiples thereof.

2. Dried yeast—U.S.P. having the following minimum vitamin content in each gram: 0.12 mg. thiamine, 0.04 mg. riboflavin and 0.25 mg. nicotinic acid.

3. Dried yeast—U.S.P. as described in (2), to which has been added riboflavin and nicotinic acid and providing for each 1 mg. of thiamine in the finished product, 1.5 to 2 mg. of riboflavin and 10 mg. nicotinic acid.

4. A concentrate of the vitamin B complex from brewer's yeast as described in (2), and providing in the recommended daily in-



take: 1 mg. thiamine (or a simple multiple thereof) and corresponding proportions of other known vitamins of yeast.

5. A concentrate of the vitamin B complex from liver containing not less than 0.25 mg. riboflavin per gram.

6. A concentrate of the vitamin B complex from brewer's yeast fortified with riboflavin and nicotinic acid and providing in the recommended daily intake: 1 mg. thiamine, 1.5 to 2 mg. riboflavin and 10 mg. nicotinic acid, or simple multiples thereof.

7. A concentrate of the vitamin B complex from rice polishings fortified with riboflavin and nicotinic acid and providing in the recommended daily intake: 1 mg. thiamine, 1.5 to 2 mg. riboflavin and 10 mg. nicotinic acid, or simple multiples thereof.

The term "concentrate" or a synonym will not be recognized for a concentrate containing thiamine if the potency of the product does not exceed 0.075 mg. per gram (or per cubic centimeter), or if it is a natural product which may have been subjected to a process of dehydration.

#### STATEMENTS REQUIRED ON MAIN LABEL

##### *For Preparations Supplying More Than Three Times the Minimum Daily Requirements*

Quantity of contents:	50 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	10 mg.
Adequate directions for use:	Dose: One tablet daily, or as prescribed by the physician. This dosage is in excess of the quantity needed for prevention of thiamine deficiency.
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

##### *For Preparations Supplying Three Times the Minimum Daily Requirements or Less*

Quantity of contents:	100 tablets
Common or usual name:	Thiamine Hydrochloride Tablets
Quantity of vitamin in tablets consumed daily:	1 mg.
Dose: This is optional	
Proportion of minimum daily requirement:	1 tablet will supply the minimum daily requirement for an adult
Name and place of business:	John Doe 550 Broad Street Chicago, Illinois

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## Decisions of General Interest

In order to aid manufacturers and distributors of medicinal articles which conform to the requirements of the Council's rules, certain statements which have been adopted by the Council are herewith presented.

### The Use of Numbers and Letters in Names

Some time ago the Council adopted the following statement expressing its attitude and requirements with regard to the use of numeral and alphabetical designations in the names of pharmaceutical products:

"Since the use of numeral or alphabetical designations in connection with drug names tends to take the emphasis away from the name and to displace the name, thus leading to confusion, the Council will not recognize the name of a drug in which the numeral or letter is an integral part of the name, except in special cases where the use of a numeral or letter seems desirable because further improvement of the product is anticipated, in which case the Council may grant a special exemption from the rule. Under this rule the use of numerals or letters in connection with the name of a product will not be permitted on labels or in advertising, unless the numeral or letter is clearly separated from and subordinated to the name by type and if feasible by position. This rule does not apply to price lists and catalogs."

The rule has been interpreted to apply also to alphabetical and numerical combinations which are sometimes used as trademarks. Such devices, when used as an integral part of a name or in a manner which would tend to promote their use as a substitute for a proper name, are held to be objectionable.

The guiding principle in the enforcement of this rule is fairly simple. The Council wishes to avoid any disposition of numbers that would tend to make them a part of the name or a substitute for it, in the minds of the prescriber or the public. It countenances their use only for the convenience of the wholesaler.

To aid manufacturers and distributors in the preparation of labels which meet the requirements of this rule, the Council offers the following examples of acceptable and unacceptable number set-ups on labels:

#### Acceptable

ELIXIR BROMIDES  
COMPOUND  
No. 42

#### Unacceptable

ELIXIR No. 42 BROMIDES  
COMPOUND

*Acceptable*

100 cc.	List No. 88
SYRUP	
EPHEDRINE COMPOUND	

*Unacceptable*

SYRUP	
EPHEDRINE COMPOUND	
No. 88	

(The typography of the numbers in the "acceptable" labels should be subordinate to that of the name itself.)

These examples do not cover all types of labels but they should serve to give some idea of what the Council is attempting to accomplish in the way of compliance with its rule prohibiting the use of numbers as integral parts of names.

These principles apply also to collateral advertising. No objection will be made, however, to a statement in the concluding paragraph of the text of an advertisement or circular to the effect that the product advertised is listed in their catalog as:

*"(Name of product) No. ...."*

## Spelling of Basic Products Having an "Amine" Group

The Council has expressed the opinion that the names of products which are basic and contain an "amine" group should end with the letter "e" and that the names of these products should also contain, if indicated, the additional term "hydrochloride" or "sulfate." Scientific nomenclature, in general, indicates a product with a name ending in "in" alone to be glucosidal in nature, whereas the ending "ine" would indicate that the compound is of a basic character. This style of nomenclature conforms with that adopted by scientific societies such as the United States Pharmacopeial Convention, the American Chemical Society and the American Society of Biological Chemists. For the past few years the Council has required adoption of this style of nomenclature for new products submitted to it; and, for the sake of uniformity it urges adoption of the final "e," where needed, for old products as well. The Council asked all firms to cooperate in adopting this style of nomenclature and revise the names of their products which are basic and contain an "amine" group to include the final "e."

## Uniform Spelling of "Ampul" and "Ampuls"

The Council voted to adopt the uniform spelling "ampul" and "ampuls" whenever reference is made in its publications to this form of container. This spelling will apply in all instances except the names of accepted preparations in the title of which the firm uses a different spelling. In such instances the Council has requested that an effort be made to obtain conformity with the preferred spelling but failure to effect the change will not be held as a bar to Council acceptance of a drug.



## Mineral Waters

The Council considers that artificial mineral waters are non-essential modifications of natural waters, and that natural mineral waters are only one feature prescribed by spas and health resorts. Mineral waters bottled for individual use are not eligible for acceptance, since there is no convincing evidence of the validity of the many therapeutic claims which are made for these preparations.

## Nasal Inhalant Preparations Containing Petrolatum

For several years brands of nasal inhalant preparations marketed in oily or ointment vehicles, consisting wholly or in part of petrolatum (principally liquid petrolatum) were included in *New and Nonofficial Remedies*. The Council reviewed the status of such preparations and is of the opinion that the repeated use of nasal inhalant preparations containing a vehicle of liquid petrolatum may lead to undesirable effects and is especially dangerous from the standpoint of lipid pneumonia; furthermore that inhalant preparations containing petrolatum offer no indispensable advantages over similar preparations containing vehicles of vegetable oils. The Council therefore omitted from N. N. R. all brands of inhalant nasal preparations containing petrolatum because of the danger of lipid pneumonia from repeated intranasal use and the fact that other safer vehicles for inhalant preparations are available. The Council has retained in N. N. R. only those oily inhalants which do not contain petrolatum, pending the development of more positive evidence concerning the irritative properties of other types of oils.

## Solutions and Suspensions for Ophthalmic Use

Before accepting any solution or suspension for ophthalmic use the Council requires that the manufacturer submit protocols to show that adequate tests for sterility are made before release of any batch of the finished product.

## Penicillin and Sulfonamide Preparations for Topical Applications and Dermatologic Preparations of Antihistamine Drugs

The Council has voted to omit from *New and Nonofficial Remedies* all penicillin and sulfonamide preparations (troches, ointments and ophthalmic ointments) designed for topical application and dermatologic preparations (creams and ointments) of antihistamine drugs because their therapeutic value appears to be outweighed by the high incidence of sensitivity reactions attending such use of these drugs. The Council, therefore, no longer considers such products for inclusion in N. N. R.

## 10 Per Cent Solutions of Sodium Morrhuate Not Acceptable

For some time the Council recognized the use of solutions of sodium morrhuate as a sclerosing agent for the injection treatment of varicose veins, and both 5 per cent and 10 per cent solutions in combination with a local anesthetic were accepted for inclusion in *New and Nonofficial Remedies*. After due consideration of the available information, the Council voted to omit all accepted brands of the 10 per cent solution of sodium morrhuate because of its questionable utility and because serious accidents have followed the use of the stronger solution in the treatment of varicose veins.

The Council authorized a revision of N. N. R. to include a recommendation for the use of a preliminary test dose as a precaution against untoward reactions with 5 per cent solutions.

## Avoidance of "Split Titles" on Labels

Several instances have arisen in which the Council has been asked to give an opinion concerning the formulation of titles on labels. The following forms are submitted as examples:

SYNTHETIN  
(Reg. U. S. Patent Office)  
HYDROCHLORIDE

SYNTHETIN  
Brand of—(generic name)  
HYDROCHLORIDE

The Council ruled that the splitting of names was objectionable, in that it might lead to confusion on the part of physicians and pharmacists, and should therefore be avoided. It was recommended that the labels given above be revised as follows:

SYNTHETIN HYDROCHLORIDE  
(Synthetin is registered in the U. S. Patent Office)

SYNTHETIN\* HYDROCHLORIDE  
\*BRAND OF—(GENERIC OR CHEMICAL NAME)

## Therapeutic Agents Derived from Animal Sources for Parenteral Use

The Council has considered the reasonable possibility that the use of therapeutic agents derived from animal sources may precipitate allergic reactions in individuals who have an allergic susceptibility to certain animals. Such allergic reactions would be most likely to occur in the use of noncrystalline preparations for parenteral use. Therefore the Council recommended that the source of animal products be declared on the label for accepted brands of noncrystalline products for parenteral injection and products for local application on freshly denuded surfaces, these to include preparations of liver extract, parathyroid solution and thromboplastic substances. This may also be applied in the future to other preparations where evidence indicates the possibility of allergic reaction.

## Variations in Labeled Content of Accepted Preparations

Preparations varying beyond 5 per cent, plus or minus, of labeled content will be accepted only if such variation may be especially justified.

### Definition of "Label" and "Labeling"

The Council voted to adopt the definition of the Federal Food, Drug and Cosmetic Act of "label" and "labeling," which is given as follows:

The term "label" means a display of written, printed or graphic matter upon the immediate container of any article.

The term "labeling" means all labels and other written, printed or graphic matter upon any article or any of the containers or wrappers accompanying such article.



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## THE COUNCIL AND OFFICIAL AGENCIES

### The Relation of the Council to Other Bodies and to Governmental Agencies Regulating Drug Products and Their Advertising

There are several official and quasi-official bodies concerned with standards, distribution, labeling and advertising of drug products. The Council on Pharmacy and Chemistry, a voluntary group with no official standing, has since its formation cooperated closely with these agencies whose objectives are similar to those of the Council. In order that the functions of these agencies may be understood and their spheres of influence as they pertain to therapeutic agents defined, the following brief descriptions of their organizations and duties are given:

*The Food and Drug Administration:* This agency is part of the United States Department of Health, Education and Welfare and is charged with the enforcement of the Federal Food, Drug and Cosmetic Act, the Caustic Poison Act, and several other statutes. The Food and Drug Administration is directed by the Commissioner of Foods and Drugs and maintains district offices in New York, Chicago and San Francisco, and station offices in Boston, Buffalo, New York, Philadelphia, Baltimore, Atlanta, Cincinnati, St. Louis, Chicago, New Orleans, Kansas City, Minneapolis, Denver, Los Angeles, San Francisco and Seattle. The administrative offices and special laboratories are located in Washington.

The Federal Food, Drug and Cosmetic Act regulates the labeling of drug products, but its authority does not extend to advertising. Seizure of offending goods, or criminal prosecution of responsible firms or persons in federal courts are among the methods used to enforce the provisions of the Act. In addition, repeated violations may be enjoined by the courts.

Violations may consist of either adulteration or misbranding or both. Adulteration refers to illegal deviations in composition of an article whereas misbranding refers to illegal statements made in the labeling or required statements omitted from the labeling.

Labeling refers not only to the labels on the immediate containers of drugs but also to circulars, pamphlets, brochures, etc., which accompany the article either physically or as a result of coming to rest with the article in the hands of the consumer.

The Food, Drug and Cosmetic Act prohibits certain things from appearing in the labeling, i.e., any statement which is false or misleading. It also requires certain things to appear in the labeling, i.e., a statement of the quantity of contents, the name and address of the manufacturer or distributor, the name and quantity of certain specific narcotic or habit-forming drugs together with a statement "Warning: May be habit-forming," the common or usual

name of each active ingredient and the quantities of certain specified ingredients, adequate directions for use unless exempted by regulation in which case the label must bear the statement "Caution, to be dispensed only by or on the prescription of a physician," and adequate warnings against possible misuse. The Act further prohibits the distribution of drugs which may be dangerous to health under the conditions of use prescribed or recommended in the labeling or of drugs which are deceptively packaged. New drugs may not be introduced into interstate commerce unless an application has been permitted to become effective. Such an application must show by adequate scientific evidence that the drug is safe for use under the conditions proposed for its use.

Certain drugs, namely, insulin, penicillin and streptomycin, are subject to special control. Samples of each batch of these drugs are examined by the Food and Drug Administration for compliance with standards set forth in regulations issued by the Administration. Each batch must be certified as complying with these standards before the batch may be distributed. Such batches of these drugs are referred to as "certified drugs."

**The Federal Trade Commission:** The Federal Trade Commission is an independent agency of the Federal Government directly responsible to the President. The Commission administers several laws, the principal one being the Federal Trade Commission Act. The principal provisions of this act have to do with the regulation of trade practices.

The Federal Trade Commission is composed of five members, appointed by the President. Not more than three of the members may be of any one political party, and the members serve for 7-year terms. The work of the Commission is organized under divisions, and that having to do with drug products is known as the Medical Advisory Division.

The principal power of the Federal Trade Commission with respect to drugs lies in Section 15 of the Federal Trade Commission Act which was amended by the Wheeler-Lea Act in 1938 giving the Commission control over the advertising of Foods, Drugs, and Cosmetics. Although the Commission has broad power to prevent the dissemination of false or misleading advertising to the general public, this power is circumscribed with respect to advertisements directed to the medical profession. The Act states "No advertisement of a drug shall be deemed to be false if it is disseminated only to members of the medical profession, contains no false representations of a material fact, and includes, or is accompanied in each instance by truthful disclosure of, the formula showing quantitatively each ingredient of such drug."

The enforcement of the Federal Trade Commission Act rests with the Commission. Trial of issues involved in violations is held before a Trial Examiner who reports his findings to the Commission. Final disposition of the case rests with the Commission. Violations of Commission "cease and desist" orders or appeals from Commission orders are considered by the Federal Courts. In many instances, controversies may be settled by stipulations between the Commission and respondents.



*The United States Public Health Service:* Among the many functions of the United States Public Health Service is the regulation of biological products. The Division of Biologics Control of the National Institutes of Health administers that part of the Public Health Service Act of 1934 which incorporates the former Viruses, Serums, Toxins and Analogous Products Act.

The control exercised by the Public Health Service Act extends only to biologic products which are defined as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man." By further definition, the term "biologic products" is extended to cover trivalent arsenical compounds. Pentavalent arsenical compounds are controlled under the Federal Food, Drug, and Cosmetic Act by administrative agreement between the Public Health Service and the Food and Drug Administration.

The control exercised by the Public Health Service over biologic products is through the inspection and licensing of establishments producing such products and by the examination and licensing of the products themselves. It is illegal, therefore, to produce any biologic product in an establishment which has not been duly licensed by the Public Health Service or to ship in interstate commerce any biologic product for which a license has not been issued and which is not effective at the time of shipment.

In order for a biologic product to be licensed under the provisions of the Public Health Service Act, it must meet the standards prescribed by the Division of Biologics Control of the National Institutes of Health, and each batch must be tested for compliance with these standards. The labels of these products must bear the proper name of the product, the name, address, and license number of the manufacturer, the lot number, and the expiration date. Under certain conditions, and in the case of certain products, additional information may be required to appear on the label.

*The United States Treasury Department:* The Bureau of Narcotics of the United States Treasury Department administers the Harrison Narcotic Act. This Act is part of the Internal Revenue Code and is primarily a taxing measure. The Act provides for the payment of certain taxes and the affixing of revenue stamps to lots of narcotic drugs.

Under the Harrison Narcotic Act, opium, cocoa leaves, or any derivatives thereof or marihuana or any derivative thereof is defined as being subject to the Act. Furthermore, by an amendment passed in 1946, the President may proclaim a drug as addiction-forming or addiction-sustaining upon a finding by the Secretary of the Treasury after due notice and an opportunity for a public hearing, and bring such a drug within the purview of the Harrison Narcotic Act. Under this provision, the drug Methadon (amidone) was proclaimed subject to the Act on July 31, 1947.

Although a tax measure, the Harrison Narcotic Act prescribes rigid controls over the transportation and distribution of narcotic drugs. Only physicians duly licensed under this Act may prescribe



these drugs, and the form of such prescriptions and their handling is set forth in considerable detail.

*The Post Office Department:* The Fraud section of the post office under the direction of the Solicitor enforces the law pertaining to the fraudulent use of the mails. The use of the United States mails is a privilege and not a right and may be denied to those who use it for the purpose of defrauding the public. Therefore, the solicitation of customers and the shipping via the mails of drugs for which fraudulent claims are made may be the basis for the issuance of a "fraud order" and the suspension of all mail service to the guilty party. Determination of the guilt is made by the Solicitor after a hearing before him in which the facts are presented. Repeated violations or efforts to avoid compliance with such fraud orders may lead to criminal prosecution in the Federal Courts.

*The United States Pharmacopeial Convention:* Under the General Committee on Revision, the United States Pharmacopeial Convention issues at 5-year intervals (formerly 10-year intervals) the United States Pharmacopeia. The United States Pharmacopeial Convention is a private body composed of representatives from medical schools, pharmacy schools, state medical associations, state pharmaceutical associations, the American Medical Association, the American Pharmaceutical Association, the American Chemical Society, and many other scientific and trade associations and also various interested federal bureaus and departments.

Under authority of the Federal Food, Drug, and Cosmetic Act, the United States Pharmacopeia is an official standard for the products described therein. Products are accepted for inclusion in the Pharmacopeia by the Committee on Revision on the basis of demonstrated therapeutic value or pharmaceutical necessity.

*The American Pharmaceutical Association:* The National Formulary is issued by the Committee on the National Formulary elected by the Council of the American Pharmaceutical Association. Admission of products to the National Formulary is based upon therapeutic value as well as upon the extent of use of the drug and the apparent need for official standards of certain drugs not necessarily widely used.

Under authority of the Federal Food, Drug and Cosmetic Act, the National Formulary is an official compendium, and drugs described therein must meet the standards set forth in that publication.

## THE METRIC SYSTEM

Formerly almost every country had its own system of weights and measures, a practice which resulted in much confusion. The one system which is used almost universally and exclusively in the exact sciences is the metric system, which is based on the decimal system and has for its units the meter and the gram.

The Council on Pharmacy and Chemistry has voted to use exclusively the metric system in any publication for which it has sole

responsibility. For this reason a table of equivalents will be provided in each book for those who are familiar only with the apothecary system.

### Table of Metric Doses with Approximate Apothecary Equivalents

The approximate dose equivalents in the following table represent the quantities which would be prescribed, under identical conditions, by physicians trained, respectively, in the metric or in the apothecary system of weights and measures.

When prepared dosage forms such as tablets, capsules, pills, etc., are prescribed in the metric system, the pharmacist may dispense the corresponding approximate equivalent in the apothecary system, and vice versa. This does not, however, authorize the alternative use of the approximate dose equivalents given below for specific quantities on a prescription which requires compounding, nor in converting a pharmaceutical formula from one system of weights or measures to the other system; for such purposes exact equivalents must be used (see U.S.P. XIV Table, page 1019).

<i>Weights</i>		<i>Weights</i>	
Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
30 Gm. = 1 ounce		40 mg. = $\frac{2}{3}$ grain	
15 Gm. = 4 drachms		30 mg. = $\frac{1}{2}$ grain	
10 Gm. = $2\frac{1}{2}$ drachms		25 mg. = $\frac{3}{8}$ grain	
7.5 Gm. = 2 drachms		20 mg. = $\frac{1}{3}$ grain	
6 Gm. = 90 grains		15 mg. = $\frac{1}{4}$ grain	
5 Gm. = 75 grains		12 mg. = $\frac{1}{5}$ grain	
4 Gm. = 60 grains (1 drachm)		10 mg. = $\frac{1}{6}$ grain	
3 Gm. = 45 grains		8 mg. = $\frac{1}{8}$ grain	
2 Gm. = 30 grains ( $\frac{1}{2}$ drachm)		6 mg. = $\frac{1}{10}$ grain	
1.5 Gm. = 22 grains		5 mg. = $\frac{1}{12}$ grain	
1 Gm. = 15 grains		4 mg. = $\frac{1}{15}$ grain	
0.75 Gm. = 12 grains		3 mg. = $\frac{1}{20}$ grain	
0.6 Gm. = 10 grains		2 mg. = $\frac{1}{30}$ grain	
0.5 Gm. = $7\frac{1}{2}$ grains		1.5 mg. = $\frac{1}{40}$ grain	
0.45 Gm. = 7 grains		1.2 mg. = $\frac{1}{50}$ grain	
0.4 Gm. = 6 grains		1 mg. = $\frac{1}{60}$ grain	
0.3 Gm. = 5 grains		0.8 mg. = $\frac{1}{80}$ grain	
0.25 Gm. = 4 grains		0.6 mg. = $\frac{1}{100}$ grain	
0.2 Gm. = 3 grains		0.5 mg. = $\frac{1}{120}$ grain	
0.15 Gm. = $2\frac{1}{2}$ grains		0.4 mg. = $\frac{1}{150}$ grain	
0.12 Gm. = 2 grains		0.3 mg. = $\frac{1}{200}$ grain	
0.1 Gm. = $1\frac{1}{2}$ grains		0.25 mg. = $\frac{1}{250}$ grain	
75 mg. = $1\frac{1}{4}$ grains		0.2 mg. = $\frac{1}{300}$ grain	
60 mg. = 1 grain		0.15 mg. = $\frac{1}{400}$ grain	
50 mg. = $\frac{3}{4}$ grain		0.1 mg. = $\frac{1}{600}$ grain	

# Table of Metric Doses with Approximate Apothecary Equivalents—Continued

<i>Liquid Measures</i>		<i>Liquid Measures</i>	
Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
1000 cc. = 1 quart		3 cc. = 45 minims	
750 cc. = 1½ pints		2 cc. = 30 minims	
500 cc. = 1 pint		1 cc. = 15 minims	
250 cc. = 8 fl. ounces		0.75 cc. = 12 minims	
200 cc. = 7 fl. ounces		0.6 cc. = 10 minims	
100 cc. = 3½ fl. ounces		0.5 cc. = 8 minims	
50 cc. = 1¾ fl. ounces		0.3 cc. = 5 minims	
30 cc. = 1 fl. ounce		0.25 cc. = 4 minims	
15 cc. = ½ fl. ounce (4 fl. drachms)		0.2 cc. = 3 minims	
10 cc. = 2½ fl. drachms		0.1 cc. = 1½ minims	
8 cc. = 2 fl. drachms		0.06 cc. = 1 minim	
5 cc. = 75 minims (1¼ fl. drachms)		0.05 cc. = ¾ minim	
4 cc. = 1 fl. drachm		0.03 cc. = ½ minim	
1 Troy or Apothecary ounce = 31.1 grams (Gm.)			
1 Avoirdupois ounce = 28.35 grams (Gm.)			
1 Avoirdupois pound = 453.6 grams (Gm.)			

*NOTE—A cubic centimeter (cc.) is the approximate equivalent of a milliliter (ml.).*



## Agents Used in Allergy

This chapter deals with prophylactic and therapeutic agents that are capable of controlling allergic phenomena. Only the histamine-antagonizing compounds are described here. Food, epidermal and other allergenic extracts are exempted from inclusion in New and Nonofficial Remedies. For reference to such products formerly included, see *N.N.R.* 1950. Sympathomimetic agents of value for this purpose are described in the chapter on autonomic drugs, and cortisone and related compounds are described in the chapter on hormones and synthetic substitutes; however, their use in the treatment of allergy will be discussed briefly in this chapter.

Agents used in the prevention and treatment of allergic manifestations may exert their action in one of several ways. These are chiefly by producing vasoconstriction, bronchial relaxation, liquefaction of bronchial secretions, sedation, and by competition with histamine, by desensitization and by modification of tissue reactivity.

**Vasoconstrictors.**—Among the most effective drugs in the symptomatic treatment of allergy are the vasoconstrictors. These include such drugs as epinephrine, ephedrine, racephedrine, phenylpropanolamine, naphazoline and amphetamine. Their action is primarily a constriction of the blood vessels and a diminution of further exudation of fluids in the tissue responsible for the particular allergic symptoms. Some of these vasoconstrictors are also good bronchodilators. The most potent of these drugs is epinephrine, which is most often used hypodermically for acute states such as asthma or acute angioneurotic edema. As its action is short, it is not practicable in such conditions as persistent urticaria. It is the most useful drug in acute allergic emergencies such as anaphylactic shock and angioneurotic edema of the larynx. Since epinephrine has a marked pressor, cardiac and cerebral excitatory action, it must be used with caution in the presence of hypertension, heart disease and some nervous manifestations. On the other hand, in acute asthma the relief obtained with epinephrine actually results in a lowering of the blood pressure and a diminution in the cardiac rate. Epinephrine solution is also useful by nebulization for the relief of asthma. It has the disadvantage, however, of causing a local vasoconstricting action in the throat and, subsequently, possible harmful effect on local tissue. In recent years this drug has been largely supplanted by isopropyl epinephrine for inhalation therapy.

**Sympathomimetics.**—Ephedrine is the most useful of the sympathomimetic drugs given orally. Its effect is of several hours duration but is not as intense as that of epinephrine. It tends

to produce the same side actions as epinephrine but in a more moderate degree. In men who might have prostatic hypertrophy it may produce difficulty in urination. Racephedrine has a less potent action than ephedrine and also lesser side actions. Phenylpropanolamine is still less potent than either of the above but can be used as a substitute when the ephedrine compounds are objectionable. These drugs, as well as naphazoline, amphetamine and others, have been employed topically, particularly in the nose, for their decongestive effect. They are useful in sinus infections for promoting drainage, in clearing the nasal passages in the acute cold and occasionally in allergy for an acute blocking of the nasal passages. They should not be used, however, in persistent nasal allergy or in other forms of chronic rhinitis. In such conditions the almost inevitable effect is to produce a rebound action of the mucosa, that is, an increased congestion after the constricting effect wears off, thus promoting a vicious cycle. In such cases it is much better to substitute the antihistamines or other oral drugs.

**Bronchodilators.**—Among the bronchodilator drugs free from vasoconstrictor action, aminophylline has been one of the most useful. It is most effective when administered intravenously, less effective rectally and least effective orally. Intravenously it will often supplement the action of epinephrine or even be effective when epinephrine has failed. In acute anaphylactic shock it should be given to supplement epinephrine therapy. Its use in conditions other than asthma or anaphylactic shock is questionable. Aminophylline may cause nervousness from cerebral stimulation. It is also a gastric irritant. Other xanthine derivatives also may be useful as bronchodilators. Other bronchodilators such as atropine or stramonium are rarely useful, probably since the effective dose cannot be achieved because of toxic effects. However, inhalation of the smoke of ignited, dried stramonium combined with potassium nitrate may produce effective relief of bronchospasm. In recent years isopropyl epinephrine has been used extensively in the relief of asthma. It is administered chiefly by inhalation of a spray or dust and at times by sublingual pellets. Its greatest advantage is that it has no pressor effect, although it does produce cardiac stimulation and cerebral excitation.

**Iodides.**—In addition to bronchospasm and edema of the mucosa, another mechanism in asthma adding to the bronchial obstruction is the hypersecretion of tenacious mucus by the bronchial glands. The iodides constitute the most effective remedy for this phase of asthma. The action of the iodides is to stimulate the bronchial glands to secrete a thin discharge, thus alleviating the plugging effect. Iodides usually are given orally in solution in the form of the potassium salt. If gastric irritation is produced, enteric-coated tablets may be employed. Although true allergic reactions to iodides may occur (consisting of fever and serious drug eruptions), most side effects are not allergic. They are of the nature of toxic reactions that would occur in virtually anyone who received large doses. In the approximate order of frequency these reactions are gastric irritation, acneiform eruptions, rhinorrhea, nasal blocking, sinus congestion, edema of the eyelids and swelling



of the salivary glands. The use of iodides for asthma in the presence of pulmonary tuberculosis has been regarded as dangerous, although the evidence for this is not conclusive. Experience indicates that there is very little possibility of such a hazard if anti-tuberculous drugs are employed concurrently. When iodides are not tolerated, expectorants such as ipecac, ammonium chloride or apomorphine may be of some help.

**Sedatives.**—Sedation in allergic disease may be employed for several purposes: to obtain rest, to allay apprehension and to counteract the stimulating effects of epinephrine, ephedrine and aminophylline. The possibility of cutaneous allergy, such as morbilliform rashes and fixed drug eruptions, from barbiturates must be considered. For sedation, particularly in asthma, chloral hydrate is more effective. Opiates are generally contraindicated in itching dermatoses and in asthma. Morphine or codeine may increase pruritus. Although morphine may allay apprehension in asthma, its depressing effect on cough and respiration may make the asthma worse. Experiments with animals indicate further that morphine is a bronchoconstrictor. Codeine and meperidine are less objectionable, but their desirability usually is outweighed by the hazards of their use.

**Hormones.**—Corticotropin, cortisone and hydrocortisone have assumed an active role in the treatment of some of the allergic diseases. Their effect is to modify the reacting tissue so that it responds less to the antigen-antibody reaction. Corticotropin must be given intramuscularly and, at times, intravenously. Cortisone may be administered orally, in addition to intramuscularly. Recently the free alcohol of cortisone also has been administered intravenously. These hormones have their chief use in treating temporary severe allergic manifestations such as acute status asthmaticus, very severe and short-term seasonal asthma and hay fever and severe drug and serum reactions of the delayed serum sickness type. Corticotropin and cortisone also have been used for protracted periods, particularly in cases of chronic asthma. The doses, methods of administration, onset of relief and precautions for use are about the same as described in the chapter on hormones and synthetic substitutes. It should be noted especially that the initial and maintenance doses of cortisone or corticotropin may have to be higher in allergic conditions than in other conditions. Withdrawal of cortisone must be gradual to avoid serious relapses. These drugs should not be used in place of simple palliative therapy, such as antihistamines, epinephrine or ephedrine, nor employed as a short cut for diagnosis of the allergy nor as a substitute for desensitization. Neither are they effective in anaphylactic reactions. These hormones have an important place in the treatment of allergy, but unless used with reason and caution they can result in more harm than good.

Hydrocortisone has been introduced in therapy more recently. The question of its effectiveness relative to cortisone when given orally is not settled. It is claimed by some that the dose required is moderately smaller. Topically, however, in ointments of 1 to 2.5 per cent strength, hydrocortisone has proved to be highly



effective in localized cutaneous lesions, such as atopic dermatitis, contact dermatitis and insect bites.

**Allergenic Extracts.**—Materials suspected of causing allergic manifestations are commonly used either for diagnostic or immunizing procedures. These consist mainly of extracts of air-borne pollens and molds, dandruffs of animals, house dust, some miscellaneous inhalants, foods and contact substances. All of the antigens (except the contactants) are extracted with an aqueous medium, usually with either saline, glycerin, dextrose or Coca's solution added, and an antiseptic. These antigenic extracts are employed diagnostically, either by scratch or intradermal technic and at times by mucous membrane testing. On the skin a diagnostic reaction consists of an urticarial wheal occurring in a few minutes. A positive reaction must be checked clinically before it can be accepted as a cause of the patient's complaint. Often the offending agent, such as feathers, dogs or food, can be removed. If this cannot be done for certain inhalants, such as pollen, mold and dust, desensitization therapy is advisable. It consists of a course of injections of the specific antigen beginning with very small doses and increasing gradually. Such desensitization is at least reasonably effective in the majority of patients, but treatment usually must be continued over a period of one to several years. In many such instances, remissions of one to several years often occur after discontinuance of therapy. Desensitization is the only therapeutic method in allergy thus far which offers the hope of lasting results.

In contact dermatitis, diagnostic tests are made by the patch methods with raw materials, such as plants and textiles, or with solutions or extracts. In plants, such as poison ivy, primrose and ragweed, it is the ether-soluble, not the water-soluble, fraction which is responsible for the dermatitis. The patch test consists of permitting the material to stay on the skin for 24 to 48 hours. A positive test consists of redness, swelling and, frequently, vesiculation. As with the scratch and intradermal tests, the patch test must be used cautiously to avoid systemic reactions.

## HISTAMINE-ANTAGONIZING AGENTS

**Actions.**—The knowledge that histamine or a histamine-like substance is released in the tissues in allergic reactions has led to the development of compounds which are histamine antagonists. Most of the ethylenediamine derivatives earlier found to possess this activity are too toxic for therapeutic use. However, several new compounds, most of them in the ethylenediamine series, are relatively nontoxic and useful in the amelioration of some allergic symptoms. These compounds must be regarded only as adjuncts to fundamental specific methods in the management of allergic conditions. The general attributes of this series of antihistaminic drugs will be briefly discussed here, the major differences being pointed out in the monographs on each drug.

These drugs, when given orally, subcutaneously, intraperitoneally or intravenously to the guinea pig, prevent histamine shock and bronchospasm from aerosolized histamine. They inhibit histamine whealing on human skin, and histamine contraction of the ileal

strip of the guinea pig in vitro. They prevent experimental histamine asthma in man and hypotension due to histamine in the cat and dog. Some actions of histamine, such as the stimulation of salivation and gastric secretion, are not inhibited by the antihistaminic drugs. These compounds also have antianaphylactic properties, but the doses required are greater than those necessary to inhibit histamine shock. All have local analgesic action and they may diminish capillary permeability to substances other than histamine. None of the antihistaminic agents, however, can take the place of vasoconstrictors, such as epinephrine and ephedrine, applied locally.

**Uses.**—The antihistamine compounds have the greatest therapeutic effect on nasal allergies; on seasonal hay fever more than on perennial vasomotor rhinitis. Relief is most probable from mild hay fever and predominantly sneezing symptoms, in the first part of the season, in a mild season, in favorable weather and in localities of low pollen or mold spore counts. Severe symptoms, advancing season, heavy season and high pollen or spore counts diminish results. The drugs are of little use in the relief of nasal blocking, particularly common at the end of the season, and postseasonally. They do not prevent or effectively relieve the asthma which frequently complicates hay fever. Their effect is entirely palliative. Hay fever is usually most effectively treated by desensitization supplemented by the use of antihistaminic drugs when needed.

The antihistaminic drugs are useful in prevention and treatment of systemic allergic reaction to injections of allergenic substances, but such remedies as epinephrine, ephedrine and aminophylline are more active and therefore more urgently indicated. In relief of the dyspnea of asthma, particularly the acute paroxysm, the histamine antagonists are ineffective except as supplements to these other remedies. Spasmodic bronchial cough without dyspnea, most frequently encountered as a manifestation of allergy in children, often responds to antihistaminic drugs, probably because of their sedative effect.

Urticaria, angioneurotic edema, serum sickness and reactions from penicillin, streptomycin, sulfonamides and other drugs are usually helped by the antihistaminic drugs. The pruritus is benefited most, edema less, and serum sickness least. Other itching skin conditions among those frequently benefited by these drugs administered internally or externally as ointments or creams are atopic dermatitis (flexural eczema), contact dermatitis, pruritus ani and vulvae, generalized pruritus and insect bites. Dosage required for relief increases with the severity of symptoms.

**Administration.**—Antihistaminic drugs are usually given orally. The range of adult doses is 2 to 100 mg., depending on tolerance, response and the individual drug. The dose should be the smallest adequate to relieve symptoms. Optimum effect usually occurs one hour after ingestion, the effect lasting from 3 to 6 hours. Some drugs may also be given intravenously or intramuscularly, but these procedures should be undertaken only in emergency and other exceptional situations. Many of the drugs cannot be given parenterally because they are irritating. Nonirritating antihistaminic drugs used as aerosols, however, help some cases of asthma



if the attack is caused by the inhalation of a specific potent antigen or following ingestion of certain foods, such as nuts, fish or mustard. Some drugs in this group also may be administered subcutaneously and in conjunction with allergenic extracts used for desensitization or other injectable remedies to which sensitivity has developed or is anticipated.

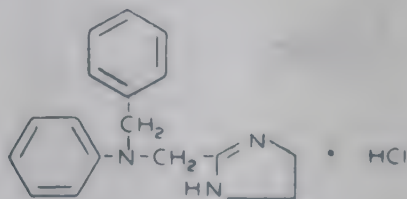
**Toxicity.**—All the antihistaminic drugs produce undesirable side reactions. The incidence and severity of these toxic actions and the dose required to produce them vary with each drug. People differ in sensitivity to the toxic actions of the group as a whole, and also in their response to particular drugs. Thus certain persons may tolerate better a drug which has a high index of toxicity than one which has a lower index.

The most common untoward action is sedation. This varies from mild sedation to deep sleep, depending on the particular drug, the individual response and the dose. Inability to concentrate, dizziness and disturbed co-ordination are related to sedative action. After the antihistaminic drug has been used for 2 or 3 days, sedation frequently disappears. If the problem is not solved in this way nor by the substitution of another antihistaminic compound, conjoint use of a cerebral stimulant such as methamphetamine or amphetamine may be advisable.

In some persons these drugs may produce such symptoms of excitation as insomnia, tremors, nervousness, palpitation and even convulsions. The side actions next in frequency are lassitude and muscular weakness, and then gastro-intestinal disturbances. The latter include various gastric discomforts, intestinal pain and diarrhea. Anorexia occurs often, as a result of both central nervous system disturbance and gastric irritation. Dryness of the mouth, throat and nose are common and, although blood dyscrasias are rare, they too have been reported. Local application of dermatologic preparations for the relief of itching associated with either allergic or nonallergic dermatoses is of doubtful value and is frequently outweighed by local sensitivity reactions to the antihistamines.

Since prolonged use of these drugs may eventually produce other toxic visceral effects, patients under continuous treatment should be examined periodically. There is also evidence that continued use of antihistaminic drugs leads to decreased effectiveness (tolerance).

**ANTAZOLINE HYDROCHLORIDE.** — Antistine Hydrochloride (CIBA). — 2-(N-Benzylanilinomethyl)-2-imidazoline hydrochloride. — The structural formula of antazoline hydrochloride may be represented as follows:





**Physical Properties.**—Antazoline hydrochloride forms white, odorless crystals with a bitter taste. It melts with decomposition between 232 and 238°. It is sparingly soluble in alcohol and water and practically insoluble in benzene and ether. A 1 per cent solution has a pH between 5.6 and 6.6.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. The therapeutic action of antazoline hydrochloride is weaker than that of most of the other antihistaminic drugs. It has particular virtues, however, in that it is milder and less irritating to tissues than other drugs of this group. Approximately 20 per cent of patients exhibit some side reactions, the most common of which are nausea and drowsiness.

Because it is less irritating, antazoline hydrochloride may be applied topically to the mucous membrane of the nose with some local effect on nasal allergy. Immediate relief is rarely obtained with topical application of solutions of the drug since active constriction of the blood vessels is lacking; such immediate relief as may occasionally be observed is probably the result of slight local anesthetic activity.

**Dosage.**—Orally, as tablets, 100 mg. is given four times daily. If adequate response is obtained, the dosage may be reduced to 100 mg. twice daily.

For nasal application, an 0.5 per cent solution in isotonic sodium chloride may be instilled in the nose, or administered intranasally by a suitable nebulizer every 3 to 4 hours. The frequency of administration should be governed by response.

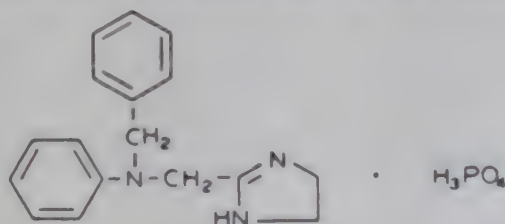
#### CIBA PHARMACEUTICAL PRODUCTS, INC.

**Nasal Solution Antistine Hydrochloride 0.5%:** 15 cc. dropper bottles. A solution containing 5 mg. of antazoline hydrochloride in each cubic centimeter.

**Tablets Antistine Hydrochloride: 0.1 Gm.**

U. S. patent 2,449,241. U. S. trademark 432,457.

**ANTAZOLINE PHOSPHATE.**—Antistine Phosphate (CIBA).—2-(N-Benzylanilinomethyl)-2-imidazoline phosphate.—The structural formula of antazoline phosphate may be represented as follows:



**Physical Properties.**—Antazoline phosphate is a white, odorless, crystalline powder with a bitter taste. It melts with decomposition between 194 and 198°. It is soluble in water, sparingly soluble in methanol and practically insoluble in benzene and ether. The pH of a 2 per cent solution is about 4.5.

**Actions and Uses.**—See the general statement on histamine-

antagonizing agents and the monograph on antazoline hydrochloride. The phosphate is preferable to the hydrochloride for ophthalmic application in the management of ocular allergies because it produces less smarting and stinging. Systemic therapy by oral administration of antazoline hydrochloride is sometimes desirable to supplement local treatment in the eye.

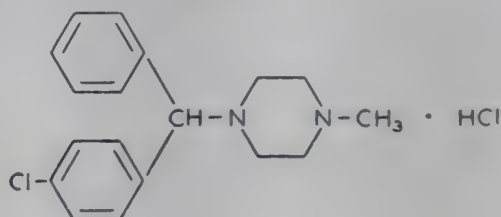
**Dosage.**—A 0.5 per cent isotonic solution of antazoline phosphate is employed for instillation in the eye. One or 2 drops are instilled in each eye every 3 or 4 hours or less frequently as required to relieve symptoms.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Ophthalmic Solution Antistine Phosphate 0.5%:** 15 cc. dropper bottles. A solution containing 5 mg. of antazoline phosphate in each cubic centimeter. Preserved with 0.0065 per cent methylparaben and 0.0035 per cent propylparaben.

U. S. patent 2,449,241. U. S. trademark 432,457.

**CHLORCYCLIZINE HYDROCHLORIDE.**—Di-Paralene Hydrochloride (ABBOTT).—1-(*p*-Chlorobenzhydryl)-4-methylpiperazine hydrochloride.—The structural formula of chlorcyclizine hydrochloride may be represented as follows:



**Physical Properties.**—Chlorcyclizine hydrochloride is a white, odorless, crystalline solid with a bitter taste. It melts between 222 and 227°. One part of chlorcyclizine hydrochloride is soluble in 1.6 parts of water, in 10.4 parts of alcohol and in 3.6 parts of chloroform, and is practically insoluble in benzene and ether. The pH of a 1 per cent solution is between 5.0 and 5.5.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. Chlorcyclizine hydrochloride has prolonged action and low incidence of toxic effects. Symptomatic benefit from this antihistamine is somewhat more erratic than from others of the group.

**Dosage.**—A dose of 50 mg. is given orally two or three times daily.

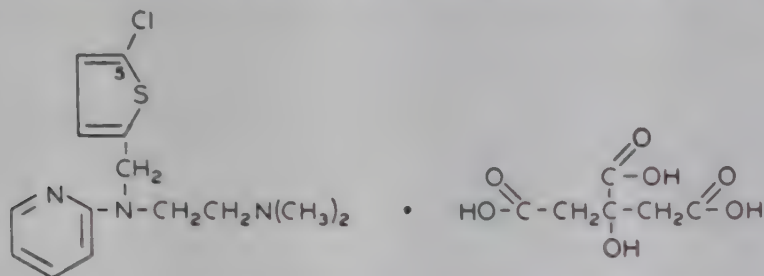
ABBOTT LABORATORIES

**Tablets Di-Paralene Hydrochloride:** 25 mg. and 50 mg.

U. S. patent 2,630,435. U. S. trademark 549,185.

**CHLOROMETHAPYRILENE CITRATE.**—Chlorothen Citrate (WHITTIER). — 2-[ (2-Dimethylaminoethyl) - 2 - (5-chlorothenylamino) ]pyridine citrate. — N,N-Dimethyl-N'-(2-pyridyl)-N'-(5-

chloro-2-thenyl)ethylenediamine citrate.—The structural formula of chloromethapyrilene citrate may be represented as follows:



**Physical Properties.**—Chloromethapyrilene citrate is a white, practically odorless solid. It melts between 116 and 118°. It is very slightly soluble in ether. The amounts which dissolve in the following solvents to form 100 ml. of solution are 2.5 Gm. in alcohol and 4.7 Gm. in water. When sodium hydroxide T.S. is added to a 1 per cent solution, the free base is obtained as an oil. The 1 per cent solution is clear and colorless, and has a pH between 3.9 and 4.1.

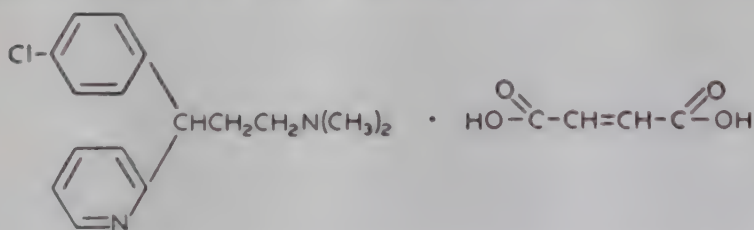
**Actions and Uses.**—See the general statement on histamine-antagonizing agents.

**Dosage.**—The average adult dose is 25 mg. administered orally.

#### WHITTIER LABORATORIES

Tablets Chlorothene Citrate: 25 mg.

**CHLORPROPHEOPYRIDAMINE MALEATE.**—Chlor-Trimeton Maleate (SCHERING). — 1-(*p*-Chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane maleate.—The structural formula of chlorprophenpyridamine maleate may be represented as follows:



**Physical Properties.**—Chlorprophenpyridamine maleate is a white, crystalline solid which melts between 130 and 135°. One part of chlorprophenpyridamine maleate is soluble in 3.4 parts of water, in 10 parts of alcohol and in 10 parts of chloroform, and is slightly soluble in benzene and ether. The pH of a 1 per cent solution is about 4.8.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. Chlorprophenpyridamine maleate has good therapeutic efficacy and low incidence of side effects. It is comparable in therapeutic efficacy to other antihistaminics although administered in very low dosage. The effect of the drug may be prolonged by administering a special repeat action tablet form



containing twice the average single dose, one-half of which is contained in an enteric-coated core to delay absorption. The drug also may be administered parenterally by intravenous, intramuscular, or subcutaneous injection whenever oral medication is not feasible or is not absorbed as rapidly as desired, and to produce a more prompt effect in allergic emergencies if it is used in conjunction with potent remedies such as epinephrine and aminophylline. A solution for injection also may be mixed with allergenic extracts for desensitization or with other compatible remedies to minimize anticipated sensitivity reactions.

**Dosage.**—The average oral dose for adults is 2 to 4 mg. A special repeat action tablet containing a total of 8 mg., half of which is enclosed by an enteric-coated core to prolong the action of the drug, may be administered to adults at intervals of 8 to 10 hours during the day and once at bedtime. The usual parenteral dose for adults is 2 to 4 mg., intramuscularly. Intravenous and subcutaneous dosages are approximately the same. Whenever possible, parenteral dosage should be governed by an initial test dose of 2 mg. to determine individual tolerance. Intravenous injection should be made slowly. Parenteral doses up to 10 mg. may be given in severe emergency cases that react favorably and do not exhibit untoward effects from prior smaller doses.

#### SCHERING CORPORATION

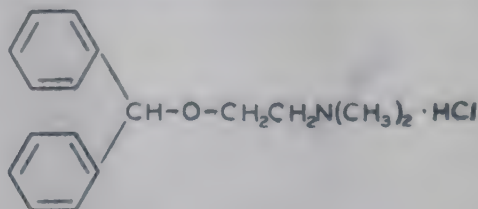
**Solution Chlor-Trimeton Maleate:** 1 cc. ampuls and 10 cc. vials. A solution containing 2 mg. of chlorprophenpyridamine maleate in each cubic centimeter. Preserved with thimerosal 1:10,000.

**Syrup Chlor-Trimeton Maleate:** 473 cc. and 3.78 liter bottles. A flavored solution containing 0.5 mg. of chlorprophenpyridamine maleate in each cubic centimeter.

**Tablets Chlor-Trimeton Maleate:** 4 mg.

**Repetabs (Repeat Action Tablets) Chlor-Trimeton Maleate:** 8 mg. U. S. patent 2,567,245. U. S. trademark 540,718.

**DIPHENHYDRAMINE HYDROCHLORIDE-U.S.P.**—Benadryl Hydrochloride (PARKE, DAVIS).—2-(Benzohydroxy)-N,N-dimethylethylamine hydrochloride. —“Diphenhydramine Hydrochloride, dried at 105° for 3 hours, contains not less than 98 per cent of C<sub>17</sub>H<sub>21</sub>NO.HCl.” U.S.P. The structural formula of diphenhydramine hydrochloride may be represented as follows:



**Physical Properties.**—Diphenhydramine hydrochloride occurs as a white, odorless, crystalline powder which slowly darkens on

exposure to light. Its solution is practically neutral to litmus paper. It is freely soluble in water, alcohol and chloroform and slightly soluble in benzene and ether.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. In addition to its antihistaminic activity, this compound has moderate antispasmodic action, but the usefulness of this effect is limited to the relief of bronchial spasm. It produces a high incidence of sedation when used in full therapeutic doses.

**Dosage.**—The average adult dose is 50 mg. orally, three or four times daily. Parenteral therapy should be used only to alleviate severe symptoms. An initial test dose of 10 mg. should be administered parenterally. If sedation is not severe, subsequent doses may be increased to 20 to 50 mg. every 2 or 3 hours.

PARKE, DAVIS & COMPANY

Capsules Benadryl Hydrochloride: 25 mg.

Elixir Benadryl Hydrochloride: 473 cc. bottles. An elixir containing 2.5 mg. of diphenhydramine hydrochloride in each cubic centimeter.

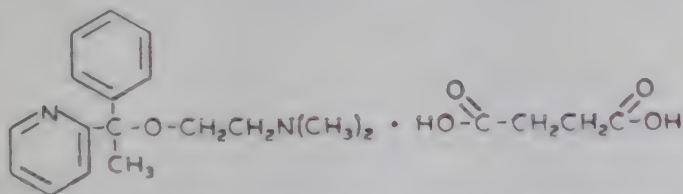
Kapseals Benadryl Hydrochloride: 50 mg.

Powder Benadryl Hydrochloride: 14.17 Gm. vials.

Solution Benadryl Hydrochloride: 10 cc. Steri-Vials. A solution containing 10 mg. of diphenhydramine hydrochloride in each cubic centimeter.

U. S. patent 2,421,714. U. S. trademark 416,252.

**DOXYLAMINE SUCCINATE.**—Decapryn Succinate (MERRELL).—2-[ $\alpha$ -(2-Dimethylaminoethoxy)- $\alpha$ -methylbenzyl]pyridine succinate—The structural formula of doxylamine succinate may be represented as follows:



**Physical Properties.**—Doxylamine succinate is a cream to white powder with a characteristic odor. It melts between 100 and 104°. It is very soluble in water, freely soluble in alcohol and chloroform and slightly soluble in benzene. The free base is obtained as an oil upon the addition of sodium hydroxide T.S. to a 5 per cent solution of doxylamine succinate. A 1 per cent solution of doxylamine succinate has a pH between 4.9 and 5.1.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. Doxylamine succinate produces a high incidence of sedation when used in full therapeutic doses.

**Dosage.**—The initial dose should be 12.5 mg. orally; this may be increased until the desired response is obtained or side effects become pronounced. The average adult dose is 12.5 to 25 mg.

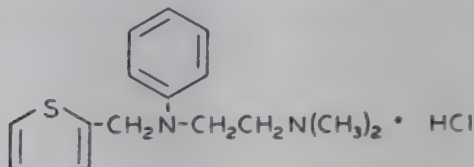
## THE WM. S. MERRELL COMPANY

**Syrup Decapryn Succinate:** 473 cc. bottles. A syrup containing 1.25 mg. of doxylamine succinate in each cubic centimeter.

**Tablets Decapryn Succinate:** 12.5 and 25 mg.

U. S. trademark 410,624.

**METHAPHENILENE HYDROCHLORIDE.**—Diatrine Hydrochloride (WARNER-CHILCOTT). — N,N-Dimethyl-N'-( $\alpha$ -thenyl)-N'-phenylethylenediamine hydrochloride.—The structural formula for methaphenilene hydrochloride may be represented as follows:



**Physical Properties.**—Methaphenilene hydrochloride is a white to pale yellow, crystalline powder with a faint odor. It melts between 184 and 189°. It is soluble in water, sparingly soluble in alcohol and chloroform and practically insoluble in ether. The free base is obtained as an oil upon adding sodium hydroxide T.S. to an aqueous solution of methaphenilene hydrochloride. A 2 per cent solution of methaphenilene hydrochloride has a pH between 4.8 and 5.6.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. Methaphenilene hydrochloride is therapeutically effective and induces low incidence of side reactions. It has a moderate tendency to cause gastro-intestinal irritation.

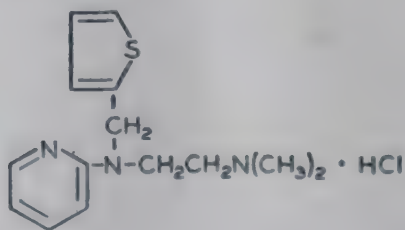
**Dosage.**—The average adult dose is 50 mg. As with other antihistaminic drugs, the dose used should be the smallest which will relieve symptoms.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

**Tablets Diatrine Hydrochloride:** 50 mg.

U. S. patent, 2,526,943. U. S. trademark 506,769.

**METHAPYRILENE HYDROCHLORIDE.**—Semikon Hydrochloride (MASSENGILL). — Thenylene Hydrochloride (ABBOTT). — 2-[(2-Dimethylaminoethyl)-2-thenylamino]pyridine hydrochloride. — N,N-Dimethyl-N'-(2-pyridyl)-N'-(2-thenyl)ethylenediamine hydrochloride.—The structural formula of methapyrilene hydrochloride may be represented as follows:





**Physical Properties.**—Methapyrilene hydrochloride is a white, crystalline powder with a faint odor. It melts between 159 and 162°. It is very soluble in water, freely soluble in alcohol and chloroform and practically insoluble in benzene and ether. The free base is obtained as an oil on the addition of 5 per cent sodium hydroxide to aqueous solutions of methapyrilene hydrochloride. A 5 per cent solution of methapyrilene hydrochloride has a pH between 5.9 and 6.4.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. The incidence of sedation is low with methapyrilene hydrochloride.

**Dosage.**—The average adult dose is 50 to 100 mg. orally.

#### ABBOTT LABORATORIES

**Tablets Thenylene Hydrochloride:** 25 and 50 mg.

U. S. patent, 2,556,566. U. S. trademark 434,475.

#### BLUE LINE CHEMICAL COMPANY

**Elixir Methapyrilene Hydrochloride:** 473 cc. and 3.78 liter bottles. An elixir containing 6.76 mg. of methapyrilene hydrochloride in each cubic centimeter.

**Tablets Methapyrilene Hydrochloride:** 50 mg.

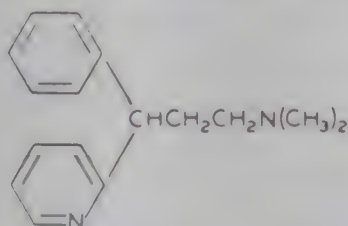
#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Methapyrilene Hydrochloride:** Bulk; for manufacturing use.

#### THE S. E. MASSENGILL COMPANY

**Tablets Semikon Hydrochloride 2%:** 50 and 100 mg.

**PROPHENPYRIDAMINE.**—Trimeton (SCHERING). — 1-Phenyl-1-(2-pyridyl)-3-dimethylaminopropane.—The structural formula of prophenpyridamine may be represented as follows:



**Physical Properties.**—Prophenpyridamine is an oily liquid with a slightly yellow color and an aminelike odor. The liquid boils around 135° at 0.5 mm. and 181° at 13 mm. It is insoluble in water, but soluble in dilute acids, alcohol, benzene, chloroform and ether.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. Prophenpyridamine is also effective in the prevention and treatment of motion sickness.

**Dosage.**—The average adult dose is 25 mg. For the prevention or

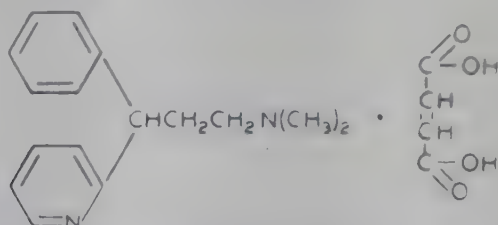
treatment of motion sickness, the adult dosage is 25 mg. three times daily.

#### SCHERING CORPORATION

Tablets Trimeton: 25 mg.

U. S. patent 2,567,245. U. S. trademark 509,760.

**PROPHENPYRIDAMINE MALEATE.**—Trimeton Maleate (SCHERING).—1-Phenyl-1-(2-pyridyl)-3-dimethylaminopropane maleate.—The structural formula of prophenpyridamine maleate may be represented as follows:



**Physical Properties.**—Prophenpyridamine maleate is a white solid with a faint aminelike odor. It melts between 104 and 108°. It is very soluble in alcohol and water, but only slightly soluble in benzene and ether. A 1 per cent solution of prophenpyridamine maleate has a pH between 4.3 and 4.9.

**Actions and Uses.**—Prophenpyridamine maleate shares the actions and uses of the base, prophenpyridamine, over which it has no therapeutic advantage. See the general statement on histamine-antagonizing agents.

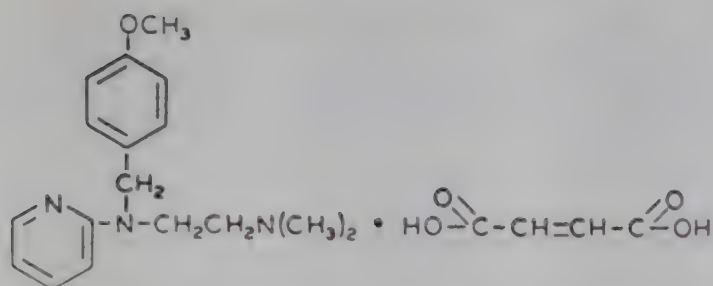
**Dosage.**—Prophenpyridamine maleate is administered orally in doses approximately 50 per cent greater than doses of the base: 1 mg. of prophenpyridamine is equivalent, on the basis of molecular weight, to approximately 1.5 mg. of prophenpyridamine maleate.

Prophenpyridamine maleate is available as an elixir palatable to children. Children under 10 years of age may be given 7.5 mg. (equivalent to 5 mg. of the base) of the elixir three or four times daily; adolescents or adults unable to swallow tablet forms of the drug may take 15 to 25 mg. or more of the salt three or four times daily.

#### SCHERING CORPORATION

Elixir Trimeton Maleate: 473 cc. bottles. An elixir containing 1.88 mg. of prophenpyridamine maleate in each cubic centimeter.

**PYRILAMINE MALEATE.**—Neo-Antergan Maleate (SHARP & DOHME).—Paraminyl Maleate (BUFFINGTON'S).—Pyramal Maleate (COLUMBUS).—Stangen Maleate (PHYSICIANS' DRUG).—Statamin Maleate (BOWMAN BROS.).—Thylogen Maleate (RORER).—2-[(2-Dimethylaminoethyl) (p-methoxybenzyl)amino]-pyridine maleate.—N,N-Dimethyl-N'-(p-methoxybenzyl)-N'-(2-pyridyl)ethylenediamine maleate. The structural formula of pyrilamine maleate may be represented as follows:



**Physical Properties.**—Pyrilamine maleate is a white, crystalline powder with a faint odor. It melts between 100 and 102°. It is very soluble in chloroform and water, freely soluble in alcohol and slightly soluble in benzene and ether. The free base is obtained as an oil on the addition of 5 per cent sodium hydroxide to an aqueous solution of pyranisamine maleate. A 5 per cent solution of pyrilamine maleate is clear and colorless, or nearly so, and has a pH between 4.5 and 5.5.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. The incidence of sedation is low with pyrilamine maleate.

**Dosage.**—The average adult dose is 25 to 50 mg. three to four times daily.

THE BOWMAN BROS. DRUG COMPANY

Tablets Statomin Maleate: 25 mg.

BUFFINGTON'S INC.

Tablets Paraminyl Maleate: 50 mg.

THE COLUMBUS PHARMACAL COMPANY

Tablets Pyramal Maleate: 50 mg.

PAUL B. ELDER COMPANY

Tablets Pyrilamine Maleate: 25 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Stangen Maleate: 25 and 50 mg.

RAYMER PHARMACAL COMPANY

Syrup Pyrilamine Maleate: 473 cc. and 3.78 liter bottles. A syrup containing 2.5 mg. of pyrilamine maleate in each cubic centimeter.

Tablets Pyrilamine Maleate: 25 and 50 mg.

WILLIAM H. RORER, INC.

Tablets Thylogen Maleate: 25 and 50 mg.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

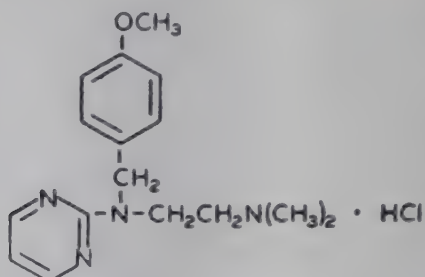
Tablets Neo-Antergan Maleate: 25 and 50 mg.

U. S. trademark 430,930.

THONZYLAMINE HYDROCHLORIDE.—Neohetramine Hydro-



**chloride (NEPERA).**—2-[(2-Dimethylaminoethyl)(*p*-methoxybenzyl)amino]pyrimidine hydrochloride. — *N,N*-Dimethyl-*N'*-(*p*-methoxybenzyl)-*N'*-(2-pyrimidyl)ethylenediamine hydrochloride. — The structural formula of thonzylamine hydrochloride may be represented as follows:



**Physical Properties.**—Thonzylamine hydrochloride is a white, crystalline powder with a faint odor. It melts between 173 and 176°. It is very soluble in water, freely soluble in alcohol and chloroform and practically insoluble in ether. The free base is obtained as an oil upon the addition of 5 per cent sodium hydroxide to aqueous solutions of thonzylamine hydrochloride. A 2 per cent solution of thonzylamine hydrochloride has a pH between 5.1 and 5.7.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. Although larger doses are required than for most other antihistaminic drugs to produce a reasonable degree and incidence of therapeutic effectiveness, the incidence and degree of side actions are less than with most other antihistaminic drugs. Its outstanding advantage is that sedation is less frequent and less severe.

**Dosage.**—The average adult dose is 50 to 100 mg.

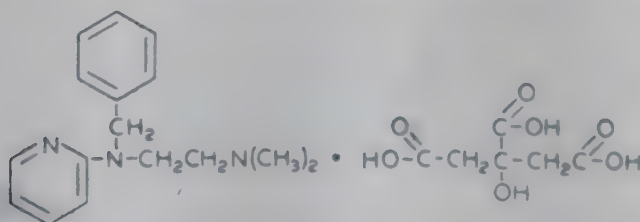
NEPERA CHEMICAL COMPANY, INC.

**Syrup Neohetramine Hydrochloride:** 475 cc. bottles: A syrup containing 6.25 mg. of thonzylamine hydrochloride in each cubic centimeter.

**Tablets Neohetramine Hydrochloride:** 25, 50 and 100 mg.

U. S. patent 2,465,865. U. S. trademark 501,673.

**TRIPLENNAMINE CITRATE.**—Pyribenzamine Citrate (CIBA).—2-[Benzyl(2-dimethylaminoethyl)amino]pyridine citrate. — *N,N*-Dimethyl-*N'*-benzyl-*N'*-( $\alpha$ -pyridyl)ethylenediamine citrate. — The structural formula of tripeleennamine citrate may be represented as follows:



**Physical Properties.**—Tripeleannamine citrate is a white, crystalline powder with a bitter taste. It melts between 106 and 110°. It is very soluble in water, freely soluble in alcohol, very slightly soluble in ether and practically insoluble in benzene and chloroform. A 1 per cent solution has a pH of about 4.25.

**Actions and Uses.**—Tripeleannamine citrate is more palatable than the hydrochloride for oral administration of the drug in liquid form; otherwise it has no advantage over the hydrochloride and provides the same antihistaminic action. See the monograph on tripeleannamine hydrochloride and the general statement on histamine-antagonizing agents.

**Dosage.**—Tripeleannamine citrate is administered in doses one-third greater than the hydrochloride because of the difference in the molecular weights of these compounds; 30 mg. of tripeleannamine citrate is equivalent to 20 mg. of tripeleannamine hydrochloride.

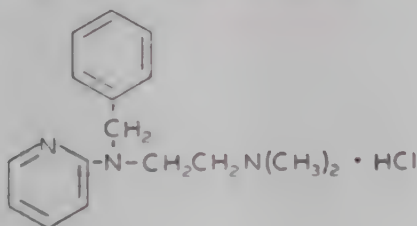
The average adult dose is 75 mg., four times daily. Infants and children usually tolerate doses of 15 to 60 mg., given at the same intervals.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Elixir Pyribenzamine Citrate:** 473 cc. and 3.78 liter bottles. An elixir containing 7.5 mg. of tripeleannamine citrate in each cubic centimeter.

U. S. patent 2,406,594. U. S. trademark 425,662.

**TRIPLENNAMINE HYDROCHLORIDE-U.S.P.**—Pyribenzamine Hydrochloride (CIBA). — 2-[Benzyl(2-dimethylaminoethyl)amino]pyridine hydrochloride.—N,N-Dimethyl-N'-benzyl-N'-( $\alpha$ -pyridyl)-ethylenediamine hydrochloride. — "Tripeleannamine Hydrochloride, dried at 105° for 3 hours, contains not less than 98 per cent of  $C_{16}H_{21}N_3 \cdot HCl$ ." U.S.P. The structural formula of tripeleannamine hydrochloride may be represented as follows:



**Physical Properties.**—Tripeleannamine hydrochloride is a white, crystalline powder which darkens slowly on exposure to light. Its solutions are practically neutral to litmus paper. One gram dissolves in 1 cc. of water, 6 cc. of alcohol, 6 cc. of chloroform and about 350 cc. of acetone. It is insoluble in benzene, ether and ethyl acetate. It melts between 188 and 192°.

**Actions and Uses.**—See the general statement on histamine-antagonizing agents. The incidence of side reactions is low; gastrointestinal irritation is common but not severe, and nervous system stimulation occurs frequently. The drug may be injected paren-

terally (subcutaneously, intramuscularly or intravenously) whenever oral medication is not feasible or to produce a more prompt response in allergic emergencies, when used as a supplement to potent remedies such as epinephrine and aminophylline. A solution for injection also may be mixed extemporaneously for subcutaneous injection with allergens or other compatible remedies to minimize anticipated sensitivity reactions.

**Dosage.**—The average adult oral dose is 50 mg., but, when indicated, larger doses of 100 to 150 mg. are tolerated by most people. For parenteral injection, a solution containing 25 mg. per cubic centimeter is administered in doses of from 12.5 to 25 mg. (0.5 to 1 cc.), two to four times daily. Depending on the parenteral route (subcutaneous, intramuscular, intravenous), the effect of such doses usually is obtained within 1 to 15 minutes and may persist for as long as 12 hours. Intravenous injection should be administered slowly with the patient recumbent. Intravenous drip using 25 mg. (1 cc.) diluted with 200 cc. of isotonic sodium chloride solution can be administered over a period of from 1.5 to 2 hours.

**CIBA PHARMACEUTICAL PRODUCTS, INC.**

**Solution Pyribenzamine Hydrochloride:** 1 cc. ampuls. A solution containing 25 mg. of tripeleminamine hydrochloride in each cubic centimeter.

**Tablets Pyribenzamine Hydrochloride:** 50 mg.

U. S. patent 2,406,594.



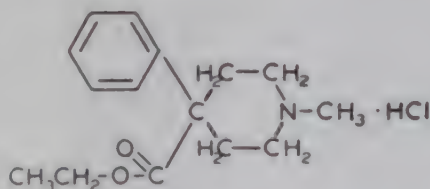
## 2

# Analgesics

Analgesic drugs relieve pain without producing loss of consciousness. The more potent of these drugs, morphine, its derivatives and newer synthetic agents, such as meperidine and methadone, may produce addiction. Some less potent analgesics were first used as antipyretics, and are sometimes described as antipyretic analgesics; among these are salicylates, cinchophen derivatives, *p*-aminophenol derivatives (acetanilid and acetophenetidin), and pyrazolon derivatives (antipyrine and aminopyrine). These milder analgesics are not addicting and some, such as acetylsalicylic acid and acetophenetidin, are considered safe for sale without a prescription. With the advent of more effective drugs for the treatment of specific infections, the use of antipyretics as such has become less important. They may be detrimental if used against a fever without knowledge of its cause.

## NONOPIATE, ADDICTING ANALGESICS

**MEPERIDINE HYDROCHLORIDE-U.S.P.**—Demerol Hydrochloride (BREON and WINTHROP-STEARNs).—Isonipeccaine.—Ethyl 1-methyl-4-phenylisonipeccotate hydrochloride.—Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride.—“Meperidine Hydrochloride, dried over sulfuric acid for 4 hours, contains not less than 97 per cent of  $C_{15}H_{21}NO_2 \cdot HCl$ .” *U.S.P.* The structural formula may be represented as follows:



**Physical Properties.**—Meperidine hydrochloride occurs as a fine, white, odorless, crystalline powder. It is soluble in water and in alcohol and sparingly soluble in ether. Aqueous solutions are acid to litmus.

**Actions and Uses.**—Meperidine hydrochloride possesses a slight atropine effect and predominant codeine-like analgesic properties. It is capable of depressing the cardiac vagus of the anesthetized animal to the point where faradic stimulation fails to elicit any cardiac effect. Such responses are reversible.

The spasmolytic action of meperidine hydrochloride is due in part to depression of the parasympathetic endings but is primarily

the result of a direct papaverine-like depression of the muscle fiber

Therapeutic doses also produce a slight sedative action. Unlike morphine, meperidine hydrochloride is not a potent hypnotic. The strength of the analgesic effect of meperidine hydrochloride in man is slightly greater than that of codeine and persists for 2 to 4 hours. It may last 6 hours with large or repeated doses.

The drug possesses moderate addiction liability evidenced by withdrawal symptoms observed in susceptible individuals. The development of tolerance to the drug has been demonstrated in man, and it may be substituted for morphine to prevent the morphine withdrawal syndrome.

The development of psychic dependence on meperidine hydrochloride is also likely since the drug produces in some individuals a euphoria which lasts for an hour or more, depending on the dose.

Meperidine hydrochloride is indicated for the alleviation of pain, particularly pain of spastic origin, and for the majority of conditions in which morphine or other opium alkaloids are generally employed. In obstetrics it may be used to lessen the severity of labor pains and, in conjunction with barbiturates, to produce obstetric amnesia.

The drug may produce contraction of the upper gastro-intestinal tract intermediate in intensity between that produced by codeine and that by morphine. Typical attacks of biliary colic have occasionally followed its use in patients with biliary tract disease. When meperidine hydrochloride is given after cholecystectomy, patients show increased pressure in the common bile duct. Thus, in the gastro-intestinal tract, the spasmolytic effect of meperidine hydrochloride is limited to the colon and lower intestine.

**Dosage.**—For most medical and surgical conditions the average adult dose of meperidine hydrochloride is 0.1 Gm., administered either intramuscularly or orally. To control pain, from 50 mg. to 0.1 Gm. may be required.

For the production of analgesia in obstetrics, 0.1 Gm. is given intramuscularly as soon as contractions occur at regular intervals. If labor is rapid or if the cervix is thin and dilated (2 to 3 cm. or more) the second dose may be given as soon as one-half hour after the first one. A third dose may be necessary an hour or two later, depending on progress.

Therapeutic doses produce a slight to moderate sedative action which shows wide individual variability, being especially prominent in the aged. Thus, barbiturates used with meperidine hydrochloride to produce amnesia are effective in considerably smaller doses than when used alone. One of the barbiturates may be given when the cervix is dilated 4 or 5 cm. or when the third dose of meperidine hydrochloride is administered. In the majority of cases this procedure will insure adequate amnesia for 4 to 6 hours.

GEORGE A. BREON & COMPANY

**Solution Demerol Hydrochloride:** 2 cc. ampuls and 30 cc. vials. A solution containing 50 mg. of meperidine hydrochloride in each cubic centimeter.

Tablets Demerol Hydrochloride: 50 mg.

WINTHROP-STEARNs, INC.

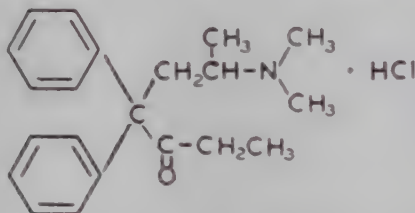
Powder Demerol Hydrochloride: 15 Gm. vials.

Solution Demerol Hydrochloride: 2 cc. ampuls, 2 cc. Ampins, and 30 cc. vials. A solution containing 50 mg. of meperidine hydrochloride in each cubic centimeter.

Tablets Demerol Hydrochloride: 50 mg. and 100 mg.

U. S. patent 2,167,351. U. S. trademark 381,130.

**METHADONE HYDROCHLORIDE.**—Adanon Hydrochloride (WINTHROP-STEARNs). — Methadon. — *d,l*-6-Dimethylamino-4,4-diphenyl-3-heptanone hydrochloride.—The structural formula of methadone hydrochloride may be represented as follows:



**Physical Properties.**—Methadone hydrochloride forms colorless crystals or a white, crystalline powder, which is odorless and bitter. It melts between 232 and 235°. It is soluble in water, freely soluble in alcohol and chloroform, practically insoluble in ether and insoluble in glycerin. It is much more soluble in diluted sulfuric acid than in diluted nitric acid and is slightly soluble in diluted hydrochloric acid. It is incompatible with alkaline solutions and with syrup of wild cherry-U.S.P. It is precipitated from solution by the common alkaloidal reagents. The pH of a 1 per cent solution of methadone hydrochloride is between 4.5 and 6.5.

**Actions and Uses.**—The term methadone refers to a mixture of the *d* and *l* isomers. The actions of methadone hydrochloride are similar to those of morphine. The *l* isomer is five times as potent as the *d* isomer. Except when taken orally, it causes less nausea and emesis than morphine and, in minimal analgesic doses causes less respiratory depression. Methadone hydrochloride seems slightly less sedative than morphine, but its action lasts longer than that of morphine, and it is better absorbed when administered orally.

Methadone hydrochloride induces addiction and, after long administration, may cause withdrawal symptoms, but they appear more slowly and are less severe than those caused by similar administration of morphine. Methadone hydrochloride may be substituted for morphine to prevent or alleviate morphine withdrawal symptoms.

Methadone hydrochloride may be used as an analgesic for moderate and severe pain. It is also antitussive, but for this purpose codeine is preferred because it has less addiction liability.

**Dosage.**—Adults, 5 to 15 mg. depending on the intensity and



etiology of the pain. The usual dose is 7.5 mg. orally every 3 to 4 hours.

When necessary, the drug may be administered parenterally either intramuscularly or subcutaneously, but because of its slight local irritant effects it should not be administered by either route in doses larger than 2.5 to 10 mg. It should not be given intravenously.

#### ABBOTT LABORATORIES

**Solution Methadone Hydrochloride:** 1 cc. ampuls and 20 cc. vials. An isotonic sodium chloride solution containing 10 mg. of methadone hydrochloride in each cubic centimeter. The 20 cc. vial is preserved with 0.9 per cent benzyl alcohol.

**Syrup Methadone Hydrochloride:** 473 cc. and 3.78 liter bottles. A syrup containing 0.34 mg. of methadone hydrochloride in each cubic centimeter.

#### S. E. MASSENGILL COMPANY

**Solution Methadone Hydrochloride:** 1 cc. ampuls and 10 cc vials. A solution containing 10 mg. of methadone hydrochloride in each cubic centimeter. The vials are preserved with 0.5 per cent chlorobutanol.

**Tablets Methadone Hydrochloride:** 2.5 mg., 5 mg. and 7.5 mg.

#### THE WM. S. MERRELL COMPANY

**Solution Methadone Hydrochloride:** 20 cc. vials. A solution containing 10 mg. of methadone hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Tablets Methadone Hydrochloride:** 5 mg.

#### STRONG COBB & COMPANY, INC.

**Solution Methadone Hydrochloride:** 1 cc. Ampins. A solution containing 5 mg., 10 mg. or 15 mg. of methadone hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

#### THE UPJOHN COMPANY

**Solution Methadone Hydrochloride:** 30 cc. vials. A solution containing 10 mg. of methadone hydrochloride in each cubic centimeter.

**Tablets Methadone Hydrochloride:** 10 mg.; for hypodermic use.

#### WINTHROP-STEARNs, INC.

**Elixir Adanon Hydrochloride:** 473 cc. bottles. An elixir containing 1 mg. of methadone hydrochloride in each cubic centimeter.

**Solution Adanon Hydrochloride:** 2 cc. ampuls and 20 cc. vials. A solution containing 5 mg. and 10 mg., respectively, of methadone hydrochloride in each cubic centimeter.

**Syrup Adanon Hydrochloride:** 473 cc. bottles. A syrup containing 0.33 mg. of methadone hydrochloride in each cubic centimeter.

Tablets Adanon Hydrochloride: 2.5 mg., 5 mg., 7.5 mg. and 10 mg.

U. S. trademark 435,101.

## OPIUM PRINCIPLES AND DERIVATIVES

Morphine is a complex derivative of phenanthrene. It contains two OH groups (one phenolic, the other alcoholic) in which the hydrogen can be replaced by either alkyl or acid radicals.

The more important alkyl ethers are the monomethyl (codeine), the dimethyl (thebaine) and ethyl-morphine. Heroin is the diacetyl ester derivative.

The nature of these radicals—acid or alcoholic, aromatic or aliphatic—modifies the actions quantitatively. Replacement of one hydroxyl by a methyl group (codeine) diminishes the narcotic and respiratory depressant actions but increases the convulsant action. When both OH groups are replaced by acids (diacetyl morphine), the narcotic effects are stronger than with codeine, and the convulsant action is weaker than with morphine. All opiate analgesics except codeine may be given by slow intravenous injection.

The central actions of all these morphine derivatives are qualitatively identical; but they present quantitative differences of some practical importance:

*Morphine* produces the strongest analgesic and hypnotic effects, and the weakest stimulation of the opium alkaloids. It causes the greatest derangement of digestion. Morphine and diacetyl morphine are most liable to produce addiction. Morphine has the longest analgesic action while diacetyl morphine has the shortest.

*Codeine* (methyl-morphine) is less narcotic, less constipating and less apt to induce tolerance and addiction. It is therefore especially valuable in cough and other conditions in which the sedative action must be continued for some time and for patients who do not tolerate morphine.

*Ethyl-Morphine* is intermediate between morphine and codeine in all respects. The hydrochloride is the most frequently used form.

*Diacetyl-Morphine* (heroin) is similar to morphine. It was originally introduced with the claim that therapeutic doses lessen the cough reflex and slow the respiration, while the inspirations are deeper and more powerful. Independent workers, however, have shown that there is no real difference from morphine in these respects. Diacetyl-morphine is as effective as morphine in cough, but not more so; it is less effective against dyspnea; and it is more liable to produce habit and toxic effects.

*Nalorphine*, although it exerts little or no analgesic effect, has been included in this section because of its chemical relationship to morphine.

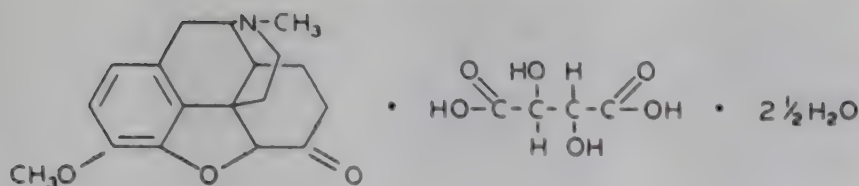
The major deficiencies of morphine as a therapeutic agent are: (1) ineffective by oral administration, (2) causes nausea, vomiting, constipation and undesirable respiratory depression and (3) quite likely to produce tolerance and addiction.

A comparative analysis of the actions of morphine with other useful, potent analgesics is presented in the accompanying table. It should be recognized that such a tabulation is neither complete nor absolutely accurate for all dosage ranges and differing conditions of administration. For example, tolerance and physical dependence can be developed by any compound in this list if large doses are administered at frequent intervals.

FOR ANALGESIA	RELATIVE Po- TENCY (ME- PERI- DINE = 1)	ORAL EFFEC- TIVE NESS	RESPIRATORY DEPRESSION	DEVELOP- MENT OF TOLERANCE: RATE	ADDIC- TION LIA- BILITY
	AVER- AGE EFFEC- TIVE DOSE, MG.	AVER- AGE DUR- ATION, HOURS	NAUSEA, VOMITING & CONSTI- PATION	EXTENT	
Racemorphan	<u>50</u> 2	<u>Good</u> 5-6	<u>Marked</u> Less marked	<u>Less rapid</u> Complete	Very great
Dihydromor- phinone	<u>50</u> 2	<u>Fair</u> 3	<u>Marked</u> Less marked	<u>Rapid</u> Complete	Very great
Metopon (Oral)	<u>33</u> 3	<u>Good</u> 3	<u>Moderate</u> Minimal	<u>Less rapid</u> Complete	Great
Heroin	<u>20</u> 5	<u>Poor</u> 2-3	<u>Marked</u> Less marked	<u>Rapid</u> Complete	Very great
Morphine	<u>10</u> 10	<u>Poor</u> 4-5	<u>Marked</u> Marked	<u>Rapid</u> Complete	Very great
Methadone	<u>10</u> 10	<u>Good</u> 4-5	<u>Marked</u> Less marked	<u>Slower</u> Less complete	Moderate
Meperidine	<u>1</u> 100	<u>Fair</u> 2-3	<u>Moderate</u> Moderate	<u>Marked</u> Incomplete	Moderate
FOR ANTITUSSIVE ACTION					
Dihydroco- deinone	<u>..</u> 5	<u>Good</u> 4-5	<u>Minimal</u> Minimal	Slow	Low
Codeine	<u>..</u> 30	<u>Good</u> 2-3	<u>Minimal</u> Minimal	Slow	Very low

**DIHYDROCODEINONE BITARTRATE.**—Hycodan Bitartrate (ENDO).—The hydrated bitartrate of dihydrocodeinone.—The structural formula of dihydrocodeinone bitartrate may be represented as follows:





**Physical Properties.**—Dihydrocodeinone bitartrate is a white, odorless, crystalline powder. It is freely soluble in water and slightly soluble in alcohol. An 0.1 M solution in freshly boiled and cooled water has a pH between 3 and 4.

**Actions and Uses.**—Dihydrocodeinone bitartrate is essentially similar in action to codeine salts, but when compared with codeine on the basis of weight it is more active and more addicting. It is useful primarily as an antitussive, in the same manner as codeine, but has no clear-cut advantage.

**Dosage.**—Adults, 5 to 15 mg., three or four times in 24 hours. The higher dosage is rarely necessary. Children 2 years of age or older may be given one-half the adult dose; younger children one-quarter the adult dose.

ENDO PRODUCTS, INC.

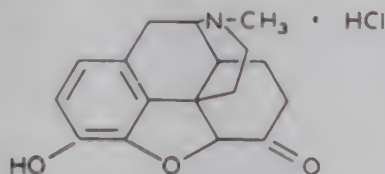
**Powder Hycodan Bitartrate:** 1 Gm., 5 Gm. and 10 Gm. bottles.

**Syrup Hycodan Bitartrate:** 475 cc. and 3.74 liter bottles. A syrup containing 1 mg. of dihydrocodeinone bitartrate in each cubic centimeter.

**Tablets Hycodan Bitartrate:** 5 mg.

U. S. trademark 399,421.

**DIHYDROMORPHINONE HYDROCHLORIDE-U.S.P.**—*Dilaudid Hydrochloride* (BILHUBER-KNOLL).—Dihydromorphinone hydrochloride differs essentially from morphine hydrochloride in that one of the hydroxyl groups of the latter has been replaced by a ketone group and the adjacent double bond has been removed by hydrogenation. The structural formula of dihydromorphinone hydrochloride may be represented as follows:



**Physical Properties.**—Dihydromorphinone hydrochloride is a fine, white, odorless, crystalline powder which is affected by light. It is soluble in water, sparingly soluble in alcohol and nearly insoluble in ether.

**Actions and Uses.**—The base dihydromorphinone has the powerful analgesic property of morphine as well as its profound depressant effect on the respiratory system. Clinically effective doses are

about one-fifth those of morphine, but the toxic dose is smaller in the same ratio. (Therapeutic index is the same for the two drugs.) While side actions, such as nausea, vomiting and constipation, occur less frequently than with morphine, the prolonged use of dihydromorphinone hydrochloride should be undertaken with just as much caution because tolerance and addiction may result. Dihydromorphinone hydrochloride is controlled by federal narcotic regulations.

**Dosage.**—Oral dosage for sedation and analgesia is 2 to 2.5 mg.; for mild pain or cough, 1.3 mg. Hypodermic dose is 1 to 2 mg.

#### BILHUBER-KNOLL CORPORATION

**Powder Dilaudid Hydrochloride:** 1 Gm., 3.54 Gm. and 14.7 Gm. packages.

**Solution Dilaudid Hydrochloride:** 1 cc. ampuls. An isotonic sodium chloride solution containing 2 mg. of dihydromorphinone hydrochloride in each cubic centimeter.

**Solution Dilaudid Hydrochloride:** 1 cc. ampuls. A solution containing 3.2 mg. of dihydromorphinone hydrochloride in each cubic centimeter.

**Rectal Suppositories Dilaudid Hydrochloride:** 2.5 mg. of dihydromorphinone hydrochloride in cacao butter base.

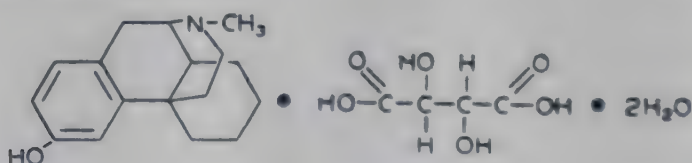
U. S. trademark 298,197.

**Tablets Dilaudid Hydrochloride:** 2.5 mg.

**Tablets Dilaudid Hydrochloride:** 32 mg.; for compounding use only.

**Tablets Dilaudid Hydrochloride:** 1 mg., 1.3 mg., 2 mg., 3.2 mg. and 4 mg. (for hypodermic use).

**LEVORPHAN TARTRATE.**—Levo-Dromoran Tartrate (HOFFMANN-LAROCHE).—Levo-3-hydroxy-N-methylmorphinan tartrate dihydrate.—The structural formula of levorphan tartrate may be represented as follows:



**Physical Properties.**—Levorphan tartrate is a white, odorless, bitter crystalline powder, with a melting point between 114 and 116°. It is very slightly soluble in chloroform and ether. The approximate amounts which dissolve at 25° in the following solvents to form 100 ml. of solution are: 0.9 Gm. in alcohol and 2 Gm. in water. Levorphan tartrate is stable to light, air, heat and moisture. The pH of the 0.2 per cent solution is between 3.4 and 4.0.

**Actions and Uses.**—Levorphan tartrate, a potent, synthetic

analgesic related chemically and pharmacologically to morphine, produces a similar intensity of analgesia in much smaller doses and seems to be somewhat longer acting. Available experimental evidence indicates that the toxicity of levorphan roughly parallels its analgesic activity. With corresponding analgesic doses, its margin of safety is approximately equal to that of morphine.

Levorphan tartrate is useful for the relief of severe pain and may be employed for the management of intractable pain caused by cancer and other tumors, severe trauma, biliary and renal colic, gangrene and myocardial infarction. It is also useful for preoperative medication and postoperative relief of pain.

Levorphan tartrate produces side effects similar to those of morphine, except that it is less likely to cause constipation. Pruritus or sweating occurs infrequently. Nausea, emesis and dizziness occur more commonly in ambulatory patients, as occurs with the use of other narcotic analgesics. The contraindications are the same as for morphine. Because the drug exhibits an addiction liability similar to that of morphine, the same precautions should be observed as for other addicting analgesics.

**Dosage.**—Levorphan tartrate is administered either orally or subcutaneously. The recommended average adult dose is 2 to 3 mg. Dosage may be subject to adjustment, in accordance with the age and weight of the patient, the severity of pain and the development of tolerance. As with other addicting analgesics, initial dosage should be as low as possible in the management of intractable pain to delay the development of tolerance.

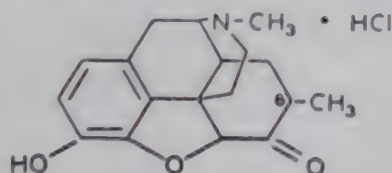
#### HOFFMANN-LAROCHE, INC.

**Solution Levo-Dromoran Tartrate:** 1 cc. ampuls and 10 cc. vials. A solution containing 2 mg. of levorphan tartrate dihydrate in each cubic centimeter. Ampul solutions are preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben; vial solutions are preserved with 0.5 per cent phenol.

**Tablets Levo-Dromoran Tartrate:** 2 mg. Each tablet contains 2 mg. of levorphan tartrate dihydrate.

U. S. patent 2,524,855. U. S. trademark 540,115.

**METOPON HYDROCHLORIDE.** — 6-Methyldihydromorphinone hydrochloride.—The structural formula of metopon hydrochloride may be represented as follows:



**Physical Properties.**—Metopon hydrochloride is a white, odorless, crystalline powder. It is very soluble in water, sparingly soluble in alcohol, slightly soluble in chloroform, very slightly soluble in ether



and insoluble in benzene. A 1 per cent aqueous solution has a pH of about 5.0.

**Actions and Uses.**—Metopon hydrochloride is a morphine derivative which is effective orally and appears to possess less undesirable side actions than the parent compound. Tolerance and dependence develop less rapidly and disappear more quickly than with morphine, but the drug must be employed with the usual care to avoid narcotic addiction.

Metopon hydrochloride is recommended only for the control of severe persistent pain. It should not be used as a preanesthetic medication because it may cause unpredictable and severe respiratory depression when used in conjunction with an inhalation anesthetic.

**Dosage.**—3 mg. is approximately equivalent in analgesic effect to 10 mg. of morphine. This dose should be repeated only on the recurrence of pain; regular administration is to be avoided, since it tends to develop tolerance and addiction. When tolerance to morphine or other narcotics is present, cross tolerance to metopon may be expected and larger doses may be required. It is desirable to keep the dose at the lowest level that will provide pain relief.

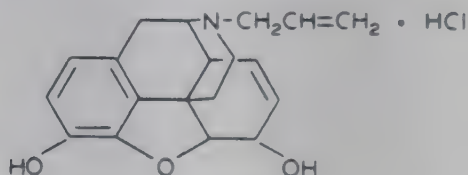
PARKE, DAVIS & COMPANY

**Capsules Metopon Hydrochloride: 3 mg.**

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Capsules Metopon Hydrochloride: 3 mg.**

**NALORPHINE HYDROCHLORIDE.**—Nalline Hydrochloride (SHARP & DOHME).—The structural formula of nalorphine hydrochloride may be represented as follows:



**Physical Properties.**—Nalorphine hydrochloride is a white, odorless, crystalline powder, with a melting point between 265 and 270°. It is completely soluble in water, very slightly soluble in chloroform and practically insoluble in ether. The amount which dissolves in alcohol to form 100 ml. of solution is 6.1 Gm. The pH of an 0.5 per cent solution is between 4.4 and 5.5.

**Actions and Uses.**—Nalorphine is a derivative of morphine and, therefore, is subject to control under the federal narcotic law. Its action, however, is considered to be pharmacologic rather than chemical, because it exerts little or no analgesic effect and antagonizes such narcotic analgesics as morphine, meperidine and methadone. Nalorphine promptly reverses the respiratory depression and increases both the minute volume and rate of respiration in patients narcotized by large doses of these compounds. It also prevents the occurrence of respiratory depression when administered

30 minutes prior to a large therapeutic dose of morphine. The drug also may reverse the fall in blood pressure, decrease in pulse pressure, cardiac arrhythmia and loss of the superficial and deep reflexes produced by these narcotic drugs. It alters the electroencephalographic pattern from that of deep sleep to that of the waking state in patients poisoned with morphine and its derivatives. It is not active against the depression produced by barbiturates, cyclopropane or ethyl ether.

Nalorphine as the hydrochloride is useful as an antidote in the treatment of accidental overdosage and to combat alarming symptoms of extreme narcosis produced by morphine and its analgesic derivatives, as well as meperidine and methadone. It is not useful as a cure or for the relief of narcotic addiction. The drug may be administered 10 minutes prior to delivery of parturient women to overcome meperidine and other narcotic-induced respiratory depression of the newborn. Its use in excessively narcotized subjects should not exclude other appropriate supportive therapy. Until the effects of long-term use become known, or are found to be harmless, it should be used only for acute conditions.

Nalorphine hydrochloride appears to be relatively safe, although the lethal dose has not been established for man. Although doses up to 40 mg. per kilogram of body weight are tolerated by experimental animals, it is considered advisable to limit single doses in man to not more than 40 mg. High dosage is usually accompanied by dysphoria, miosis, pseudoptosis, lethargy, mild drowsiness and sweating. Occasionally nausea, heaviness in the limbs and hot and cold flashes occur. Pallor, similar to that which accompanies intravenous injection of morphine, is sometimes observed. In morphine addicts, administration of the drug may be followed by typical abstinence changes, such as yawning, rhinorrhea, lacrimation, goose flesh, vomiting and restlessness.

**Dosage.**—Nalorphine hydrochloride is administered as a solution by injection intravenously, intramuscularly or subcutaneously, depending on the rapidity of the action desired. Intravenously, the usual adult single dose is 5 to 10 mg., repeated in 10 to 15 minutes if adequate increase in pulmonary ventilation is not obtained. The effect of the drug lasts from 2 to 3 hours and the total dosage to be given depends on the degree and duration of the depression. In severe cases of poisoning, doses as high as 40 mg. may be employed.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Solution Nalline Hydrochloride:** 1 and 2 cc. ampuls. A solution containing 5 mg. of nalorphine hydrochloride in each cubic centimeter. Stabilized with 0.2 per cent sodium bisulfite and buffered with 1.5 per cent sodium citrate.

# 3

## Anesthetics

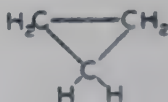
### GENERAL ANESTHETICS

General anesthetics progressively depress the central nervous system. Many of them, administered in moderate doses, induce analgesia before loss of consciousness occurs. The various reflex mechanisms are likewise inhibited in orderly progressions characteristic of each drug. This process is reversible by withdrawal of the agent.

Such drugs must enter the blood stream to be carried to the nervous system. Portals of entry are the lungs (inhalation); the gastro-intestinal tract (oral or rectal administration); direct intravenous injection. Certain agents may be given by any of the three routes (e.g. ether).

The effect of these drugs is estimated largely on the basis of changes in the various reflexes as the concentration increases in the central nervous system. General anesthesia is thus divided into stages and planes. Some drugs formerly looked upon as hypnotics are now used in much larger doses as general anesthetics (e.g. barbiturates). There can be no sharp delineation between hypnotics, sedatives and general anesthetics since effects are dependent upon the size of the dose as well as upon the pharmacologic characteristics of the drug. For this reason, so-called basal anesthetics are described along with the general anesthetics.

**CYCLOPROPANE-U.S.P.**—Cyclopropanum.—Trimethylene.—“Cyclopropane contains not less than 99 per cent by volume of  $C_3H_6$ .” *U.S.P.* The structural formula of cyclopropane may be represented as follows:



**Physical Properties.**—Cyclopropane is a colorless gas of characteristic odor, resembling that of petrolatum benzin, and having a pungent taste. One volume of cyclopropane dissolves in about 2.7 volumes of water at  $15^\circ$ . It is freely soluble in alcohol and soluble in fixed oils.

**Actions and Uses.**—Cyclopropane is the most powerful of the gaseous anesthetic agents; concentrations are from 15 per cent of cyclopropane and 85 per cent of oxygen up to the rarely and briefly



used 40 per cent of cyclopropane and 60 per cent oxygen. It should be noted, however, that only 3.5 per cent (by volume) of ether is required to induce the same plane of anesthesia that is induced with 20 per cent (by volume) of cyclopropane. Thus 96.5 per cent of oxygen may be used with ether, while only 80 per cent may be used with cyclopropane, for this particular depth of anesthesia. The high anesthetic potency of cyclopropane as compared with other hydrocarbons is advantageous because high concentrations of oxygen may be used. The rate of diffusion of cyclopropane is about twice that of ethylene. Cyclopropane is eliminated less rapidly than ethylene but much faster than ether. Induction and recovery with cyclopropane are therefore slower than with ethylene but more rapid than with ether.

Cyclopropane affects the autonomic tissue of the heart more than ether or chloroform. In high concentrations it heightens the irritability of this tissue and induces predisposition to cardiac arrhythmias. This effect is enhanced by the simultaneous use of epinephrine. For these reasons the pulse must be carefully observed and the use of sympathomimetic drugs avoided during cyclopropane anesthesia. Cyclopropane, unlike many other general anesthetic agents, does not stimulate respiration, and for this reason preoperative sedation with respiratory depressants must be used with caution. Since the signs of Guedel for other anesthetic agents do not apply to cyclopropane, familiarity with the signs of the stages of anesthesia for cyclopropane is absolutely essential in the administration of this agent.

Cyclopropane-oxygen mixtures are more explosive than other anesthetic-oxygen mixtures. Careful operating room technic should be observed to avoid production of electrostatic sparks; open flames and cautery should be handled with the same precautions as those for other explosive or inflammable anesthetics.

The advantages of cyclopropane consist in its effectiveness in concentrations which provide an adequate supply of oxygen and less excitement during induction. Its disadvantages include explosibility when oxygen-rich mixtures are employed, lack of respiratory stimulation, difficulty in detection of the planes of anesthesia by those unfamiliar with its administration, occasional laryngospasm, and tendency to produce cardiac arrhythmias, postanesthetic headache and poor muscular relaxation.

**Dosage.**—Cyclopropane is furnished in compressed form in metal containers. For use the gas is passed into a closed circuit inhalation apparatus and administered by inhalation from a rebreathing bag, always with the admixture of oxygen. The concentration employed varies from 15 to 40 per cent, but should probably not exceed 30 per cent. The remainder of the mixture should consist of a minimum of 20 per cent oxygen, but oxygen should be supplied in quantities adequate for physiologic needs. When other anesthetics are also used in combination, less cyclopropane is required.

**Caution.**—*Cyclopropane is flammable and its mixture with oxygen or air may explode when brought in contact with a flame or other causes of ignition.*

OHIO CHEMICAL & SURGICAL EQUIPMENT CO.

**Cyclopropane:** 151.4 liter, 378.5 liter and 870.6 liter cylinders.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Cyclopropane:** 151.4 liter, 378.5 liter and 757 liter cylinders.

**TRIBROMOETHANOL-U.S.P. — Avertin (WINTHROP-STEARNs).—**  
Tribromoethyl Alcohol. "Tribromoethanol dried over sulfuric acid for 4 hours contains not less than 99 per cent of  $C_2H_3Br_3O$ ." *U.S.P.* The structural formula of tribromoethanol may be represented as follows:



**Physical Properties.**—Tribromoethanol occurs as a white, crystalline powder, with a slight aromatic odor and taste. It is unstable in air. Both aqueous and alcoholic solutions of tribromoethanol decompose on exposure to light. One gram of tribromoethanol dissolves in about 35 cc. of water at 25°. It is very soluble in amylene hydrate.

**Actions and Uses.**—Tribromoethanol is administered rectally as a solution in amylene hydrate for basal anesthesia. Dosage should not be sufficient to cause complete anesthesia. Basal narcosis with a solution of tribromoethanol diminishes the amount of inhalation anesthetic necessary to establish and maintain complete anesthesia. A prolonged period of sleep usually follows termination of inhalation anesthesia; during this afterperiod careful nursing care and continuous vigilance are necessary to maintain an open airway and to prevent the cyanosis and respiratory failure which sometimes follow. Ephedrine, caffeine with sodium benzoate and oxygen therapy are effective antidotes against respiratory and circulatory depression occurring from tribromoethanol.

Tribromoethanol is useful in the control of convulsive conditions such as tetanus. In tetanus it is used (for several days, if necessary) in repeated doses in conjunction with administration of tetanus antitoxin. It must be remembered, however, that there is danger of profound respiratory depression.

Contraindications to the use of tribromoethanol include liver or kidney dysfunction, cardiac disease, hypertension, hypotension, old age, shock or dehydration, sepsis, toxemia, severe pulmonary tuberculosis, empyema, decreased vital capacity, predisposition to respiratory obstruction, hypothyroidism, obesity, asthenia, cachexia, anemia, ileus, pathology of the colon or rectum, enteritis and acidosis.

**Dosage.**—For each kilogram of body weight, rectally, 60 mg., *U.S.P.*

Solutions of tribromoethanol are administered rectally in 2.5 per cent solution in warm distilled water at a temperature not exceed-



ing 40°. A small quantity of the solution should be tested just before administration with the congo red indicator supplied with the preparation. The color of the solution should match that of an equal amount of distilled water containing an equal quantity of the congo red indicator. If the colors do not match, the presence of irritant hydrobromic acid and *di*-bromacetaldehyde is indicated, and the solution should be discarded.

The ordinary maximum dose for basal anesthesia is 80 mg. of tribromoethanol (40 mg. of amylene hydrate) per kilogram of body weight. The dose for young, vigorous persons may sometimes be increased to 90 or 100 mg. of tribromoethanol. A dose of 30 to 50 mg. per kilogram is usually sufficient for amnesia and is not accompanied by depression of the respiration or circulation. As the amylene hydrate adds materially to the narcotic effect, it should be remembered that, with each dose of tribromoethanol, half this dose by weight of amylene hydrate is administered.

The total amount administered should not exceed 6 to 8 Gm. of tribromoethanol for women, and 9 to 10 Gm. for men, regardless of weight. Dosage tables are supplied by the firm.

*Solutions of tribromoethanol should never be employed by those inexperienced in its use except under expert supervision.*

**"Caution.**—*The total amount administered should not exceed 8 Gm. for women or 10 Gm. for men, regardless of body weight."* U.S.P.

#### WINTHROP-STEARNs, INC.

**Solution Avertin with Amylene Hydrate:** 25 cc. and 100 cc. bottles. A solution containing 1 Gm. of tribromoethanol and 0.5 Gm. of amylene hydrate in each cubic centimeter.

U. S. trademark 233,204.

**VINYL ETHER-U.S.P.**—**Vinethene** (SHARP & DOHME).—"Vinyl Ether for anesthesia consists of about 96 per cent of  $C_4H_6O$  and about 4 per cent of dehydrated alcohol. It may contain 0.025 per cent of a harmless preservative." U.S.P. The structural formula of vinyl ether may be represented as follows:



**Physical Properties.**—Vinyl ether occurs as a clear liquid having a characteristic odor. It is colorless or has a slight purple fluorescence derived from the preservative. It boils between 28 and 31°. It is slightly soluble in water but is miscible with alcohol, acetone, chloroform and ether.

**Actions and Uses.**—Vinyl ether is an inhalation anesthetic to be used for short anesthesia or induction. Its action is more rapid than that of ether, U.S.P. Since the safety zone of surgical anesthesia is narrow, only constant close observation of the patient will enable



the anesthetist to avoid dangerous overdosage. Properly watched, this rapid induction and recovery are of advantage in short anesthetics. The patient is completely oriented and ambulant within a few minutes. To prevent recovery before the surgical procedure is completed, vinyl ether must be administered continuously.

The anesthetist should familiarize himself thoroughly with the properties of vinyl ether before employing it. The eye signs which indicate stages of other anesthetics are entirely unreliable in vinyl ether anesthesia. The most important signs in determining the extent of the anesthesia are the rate, depth, regularity and smoothness of respiration. Although there is occasionally an increased secretion of mucus during maintenance even when atropine is administered, postoperative complications are infrequent. Nausea and vomiting occur in about 5 per cent of patients and muscular relaxation is often poor. Vinyl ether is irritating to the skin, especially when combined with pressure (as finger pressure or holding the mask too tight). A light film of petrolatum or other lubricant should be applied to the skin of the patient's face.

Under no circumstances should the anesthetic be pushed, and if proper relaxation and anesthesia are not obtained with low concentrations other agents should be employed. Overdosage is likely to cause anoxemia, cyanosis and respiratory failure. Under such circumstances the anesthetic must be discontinued, oxygen administered with artificial respiration, and measures taken to stimulate respiration and provide an adequate airway between the lungs and the atmosphere. The explosive and fire hazards of vinyl ether are equal to those of ether, U.S.P.

Vinyl ether is intended primarily for use in minor surgical operations of short duration, and in dentistry where gas anesthesia is not available. It is also useful as an induction anesthetic, particularly in children. It has been extensively used during postpartum obstetric procedures. Its rapid action with depression of fetal respiratory movements before producing analgesia in the mother practically precludes its use during labor.

As with most other anesthetic agents, age, cardiovascular disease, renal insufficiency or hepatic damage, particularly the latter, are contraindications. It may be administered by the open drop, semi-open drop or closed machine method with soda lime absorption technic. The open drop method is preferable for short anesthesia. Adequate oxygen or air supply and an unobstructed airway are essential.

*Caution.*—Vinyl ether is flammable and deteriorates on exposure to air and light. It must be preserved in tight containers of not more than 200 cc. capacity and is not to be used if the original container has been open longer than 48 hours.

SHARP & DOHME, DIVISION OF MENCK & COMPANY, INC.

Vinethene: 10 cc. vials and 25 cc., 50 cc. and 75 cc. bottles. Packaged with plastic dropper.

U. S. patents 2,844,800, 2,844,801 and 2,895,593. U. S. trademark 312,453.

## LOCAL ANESTHETICS

Methods of producing local anesthesia (that confined to a restricted area) vary with the site of application and the technic of administration. Certain drugs (e.g. cocaine, tetracaine) are effective in topical application to mucous membranes, for surface anesthesia. Rarely used today are agents which produce freezing temperature to lower sensibility to pain (ethyl chloride, solid carbon dioxide) and protoplasmic poisons (phenol).

Local anesthesia produced by injectable compounds is designated according to the technic or anatomic site: Infiltration is injection directly into the area which is painful or subjected to surgical trauma, or nerve block injection in proximity to specific nerve trunks supplying a particular anatomic site. Particular block injections are designated according to the point chosen for interruption of nerve transmission. Two of these are: *spinal* (within the dural membrane surrounding the spinal cord and nerve roots); *extra dural or epidural* (solutions deposited immediately outside the dural membrane, and within the bony spinal or caudal canals), other blocks are designated according to their location along the course of nerve trunks on their way to the peripheral tissues.

To combat the vasodepressor effects of the local anesthetics, especially when they are injected centrally (spinal or epidural) long-acting vasoconstrictor agents (e.g. ephedrine) may be injected intramuscularly or intravenously for their systemic effect.

Certain local anesthetics cause vasoconstriction in the area applied (cocaine), others do not (tetracaine). For topical application and injection, epinephrine (or a similar less toxic vasoconstrictor agent, e.g. phenylephrine) is usually added in the preparation of solutions to impede rapid systemic absorption. Concentration of such agents in solutions to be injected should be kept at the minimum effective level (usually from 1 part in 130,000 to 1 part in 520,000 in the case of epinephrine). (See sympathomimetic agents in the chapter on autonomic drugs.)

The technical details of preparation and control of solutions to be injected, especially within the subdural or epidural spaces, are intricate and exacting. They should be acquired from authoritative source books and from instruction by experienced anesthetists. Details of dosage of any local anesthetic should be modified for different applications.

All local anesthetic agents are toxic and the tolerance of patients varies. Safe dosage is therefore limited for each drug, and administration must be individualized. Choice of drug, concentration, rate and location of injection, along with age, emotional and physical status of the patient, are a few of the factors involved. *One should use the smallest amount of the least toxic drug that will serve the purpose, if reactions are to be avoided.* The use of barbituric acid derivatives as premedication is advisable to prevent or decrease toxic reactions.

Accidental vascular injections are relatively frequent even in the practice of the most skillful anesthetist. Extreme caution is also



imperative when any local anesthetic is applied under conditions in which trauma to mucous membrane is likely to occur. Hence, when local anesthetic drugs are being used, it is in the interest of safety to have instantly available (a) oxygen and the means of inflating the lungs with it and (b) a quick-acting barbituric acid compound prepared for intravenous administration. Local anesthetic solutions are too dangerous to be applied to the traumatized urethra; general or spinal anesthetics should be employed. Lidocaine 1 per cent, lidocaine gel, and piperocaine have been instilled into the urethra and bladder with good results, but such use of these drugs must be undertaken with extreme caution.

A special dosage form of local anesthetic solutions rendered hyperbaric by addition of dextrose may be employed in low spinal or saddle block anesthesia. As the solution is heavier than spinal fluid it tends to sink to the most dependent portion of the spinal canal. The technic of administration must take this characteristic into consideration since prolonged pooling of these concentrated solutions of anesthetics may cause extensive nerve damage. This may be avoided by proper timing in the positioning of the patient. Low spinal or saddle block anesthesia is of value in obstetrics for vaginal deliveries, in rectal surgery and in genito-urinary procedures not involving abdominal surgery.

A special dosage form of local anesthetic may be used to induce continuous caudal analgesia in obstetric cases. *The procedure must be undertaken only by skilled specialists and carried out with great caution because there is great danger of infection.* Two techniques have been used; one involves the use of a special malleable needle, the other a ureteral catheter. When the special needle is used, great care must be taken that the portion of the needle which lies outside the skin is protected, so that movement of the patient will not force the needle up into the caudal canal, against bone or into a blood vessel or dura. The patient should lie on her side. The needle must be protected against breakage. If it breaks within the canal, it must be removed within a few hours.

If a urethral catheter is to be employed, entry into the caudal canal should be made with a needle no larger than 15 gauge. If it is necessary to use a needle as large as 13 gauge and the caudal canal is not entered on the first attempt, the method should be discarded; otherwise infection is almost certain to occur. Extreme care must be exercised to prevent infection, one of the great dangers encountered in continuous caudal analgesia. Emergency measures to control untoward reactions should be immediately available. Soluble barbiturates (e.g. hexobarbital sodium-N.N.R., thiopental sodium-U.S.P.) are useful to control convulsions. Oxygen should be immediately accessible.

Continuous caudal analgesia is contraindicated in the presence of placenta praevia, inertia uteri, uncontrollable hysteria, anomalies of the sacrum and disproportion of child and pelvis. History of sensitivity to local anesthetics is another contraindication. Continuous caudal anesthesia is not suitable for difficult forceps rotation or version because in such cases complete relaxation of the uterus is imperative.



The slight solubility of some of these anesthetics renders them unsuitable for injection, but their slow absorption renders them safer, especially for ulcers, wounds and mucous surfaces. The anesthesia which they induce is usually not so complete as that induced by the soluble local anesthetics, but it is more lasting. They are practically nonirritant and nontoxic. Ethyl aminobenzoate (benzocaine, anesthesin) and orthoform are about equally effective through intact mucous membranes; butyl aminobenzoate (butesin) is more effective than either.

Many, if not all, local anesthetics occasionally give rise to dermatitis. When this is severe, the use of the anesthetic should be discontinued.

**BUTETHAMINE FORMATE.**—**Monocaine Formate** (NOVOCOL).—2-Isobutylaminoethyl *p*-aminobenzoate formate.—The formic acid salt of the ester formed from *p*-aminobenzoic acid and the *N*-isobutyl derivative of ethanolamine. The structural formula of butethamine formate may be represented as follows:



**Physical Properties.**—Butethamine formate forms odorless, white crystals, which melt between 136 and 139°. It is freely soluble in alcohol and water, very slightly soluble in benzene and slightly soluble in chloroform and ether. The pH of a 1 per cent solution is about 6.1.

**Actions and Uses.**—Butethamine formate is proposed for use in spinal anesthesia. Its action is qualitatively identical with that of procaine, but it produces about one-third greater anesthetic and toxic effects.

**Dosage.**—For spinal anesthesia the dosage depends on the speed and mode of injection, the size of the patient and the length of the operative procedure to be performed. Because it is one-third stronger, the dosage of butethamine formate should be about three-fourths of the usual dosage of procaine.

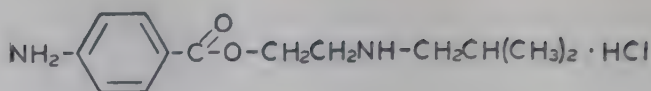
NOVOCOL CHEMICAL MFG. COMPANY, INC.

**Crystals Monocaine Formate:** 50, 100, 150 and 200 mg. ampuls; 300 and 500 mg. containers (fractional doses). For spinal anesthesia.

**Solution Monocaine Formate 5%:** 2 cc. ampuls. A solution in sterile distilled water containing 50 mg. of butethamine formate in each cubic centimeter. For spinal anesthesia.

U. S. patent 2,139,818. U. S. trademark 353,653.

**BUTETHAMINE HYDROCHLORIDE.**—**Monocaine Hydrochloride** (NOVOCOL).—2-Isobutylaminoethyl *p*-aminobenzoate hydrochloride.—The structural formula of butethamine hydrochloride may be represented as follows:



**Physical Properties.**—Butethamine hydrochloride is a white, odorless, crystalline powder with a bitter taste and anesthetizing effects. It melts between 192 and 196°. It is sparingly soluble in water, slightly soluble in alcohol and chloroform, very slightly soluble in benzene and practically insoluble in ether. The pH of a 1 per cent solution is about 4.7.

**Actions and Uses.**—Butethamine hydrochloride is a local anesthetic similar to procaine hydrochloride. It is used for nerve block anesthesia in dentistry and other surgery. Present evidence does not warrant its use for topical or surface anesthesia of mucous or other membranes. Its effects, either with or without the addition of epinephrine hydrochloride, are qualitatively identical with those of procaine. Quantitatively, butethamine hydrochloride has about one-third more anesthetic and toxic potency than procaine (i.e., a butethamine hydrochloride solution of three-fourths the concentration of a procaine solution is of equal effectiveness).

**Dosage.**—For dental or other minor surgery, a 1 per cent solution with epinephrine 1:75,000 may be injected to obtain nerve block anesthesia. In major surgery or other procedures requiring nerve block anesthesia equivalent to that produced by 2 per cent procaine, a 1.5 per cent solution of butethamine hydrochloride with epinephrine 1:100,000 may be used. (See caution under the general statement on local anesthetics.)

NOVOCOL CHEMICAL MFG. COMPANY, INC.

**Solution Monocaine Hydrochloride 1% with Epinephrine 1:75,000:** 2 cc., 3 cc. and 5 cc. ampuls; 2 cc., 2.5 cc. and 5 cc. Anestubes (syringe cartridge); 2.5 cc. and 5 cc. Novampuls (ampul type syringe); and 30 cc., 60 cc. and 120 cc. bottles. A solution in sterile distilled water containing 10 mg. of butethamine hydrochloride, 0.01 mg. of epinephrine, 1.5 mg. of sodium bisulfite, and 6.5 mg. of sodium chloride in each cubic centimeter.

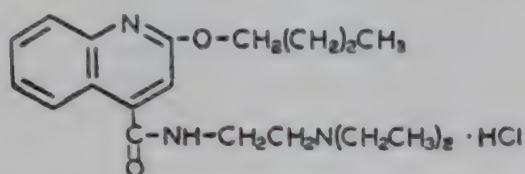
**Solution Monocaine Hydrochloride 1.5% with Epinephrine 1:100,000:** 2 cc., 3 cc. and 5 cc. ampuls; 1 cc., 2 cc., 2.5 cc. and 5 cc. Anestubes (syringe cartridge); 2.5 cc. and 5 cc. Novampuls (ampul type syringe); 60 cc. and 120 cc. bottles. A solution in sterile distilled water containing 15 mg. of butethamine hydrochloride, 0.01 mg. of epinephrine, 1.5 mg. of sodium bisulfite, and 4.5 mg. of sodium chloride in each cubic centimeter.

U. S. patent 2,139,818. U. S. trademark 353,653.

**DIBUCAINE HYDROCHLORIDE-N.F.**—Nupercaine Hydrochloride (CIBA). — 2-Butoxy-N-(2-diethylaminoethyl)cinchoninamide hydrochloride.—“Dibucaine Hydrochloride contains not less than 88.5 per cent and not more than 90.5 per cent of  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_2$  and not less than 9.5 per cent and not more than 9.7 per cent of HCl.”



*N.F.* The structural formula of dibucaine hydrochloride may be represented as follows:



**Physical Properties.**—Dibucaine hydrochloride occurs as fine, white, lustrous crystals or as a white powder. It is odorless and quite hygroscopic. It exhibits a bitter, acrid taste with a prolonged local anesthetic action and is sensitive to light. One gram of dibucaine hydrochloride dissolves in about 2 cc. of water. It is freely soluble in alcohol, in acetone and in chloroform but only slightly soluble in cold benzene, in ethyl acetate and in toluene.

**Actions and Uses.**—Dibucaine hydrochloride is a local anesthetic which acts like cocaine when applied to mucous surfaces and like procaine or cocaine when injected, the action being prolonged. Dibucaine hydrochloride is about five times as toxic as cocaine when it is injected intravenously into animals, and its anesthetic activity is correspondingly greater than that of cocaine when it is applied to a mucous surface; injected subcutaneously it is many times more active than procaine hydrochloride. It has caused necrosis of tissue in one case and a condition resembling gangrene with recovery in another. Death has occurred after the subcutaneous injection of 135 cc. of a solution of 1:1,000. Weak solutions (1:2,000) cause slight temporary vascular dilatation (prevented by the addition of epinephrine hydrochloride), followed by constriction.

A 1:400 solution of dibucaine hydrochloride made hyperbaric with 5 per cent of dextrose may be used for low spinal or saddle block anesthesia.

**Warning:** Pooling of this concentrated solution of dibucaine hydrochloride in the conus may cause extensive nerve damage. Therefore the patient should not be kept in the sitting position for more than one minute following the introduction of the agent into the spinal canal.

**Dosage.**—An 0.25 per cent solution made hyperbaric with 5 per cent of dextrose is used for the production of low spinal or saddle block anesthesia; the dosage should be limited to 2.5 to 3.0 mg. Aqueous solutions of dibucaine hydrochloride should be prepared with distilled water, as the salts present in the tap water of many localities may precipitate the free base. Alkali-free glass should be used in the preparation of dibucaine hydrochloride solutions. (See caution in the general statement on local anesthetics.)

Other dosage forms of this drug have been exempted and were last described in N. N. R. 1952.

CIBA PHARMACEUTICAL PRODUCTS, INC.

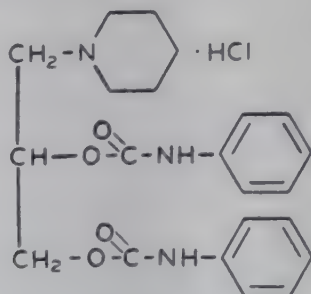
Heavy Solution Nupercaine Hydrochloride with Dextrose: 2 cc.



ampuls. A solution containing 2.5 mg. of dibucaine hydrochloride and 50 mg. of dextrose in each cubic centimeter.

U. S. patent 1,825,623. U. S. trademark 266,366.

**DIPERODON HYDROCHLORIDE.**—**Diorthane Hydrochloride** (MERRELL).—3-(1-Piperidyl)-1,2-propanediol dicarbanilate hydrochloride.—The structural formula of diperodon hydrochloride may be represented as follows:



**Physical Properties.**—Diperodon hydrochloride is a fine, white, crystalline, odorless powder. It produces a bitter taste followed by a sense of numbness. It is stable in air at ordinary temperatures. It melts with decomposition between 195 and 200°. From aqueous solutions, alkali carbonates and hydroxides precipitate the free base as a colorless oil, which does not solidify under ordinary conditions. Diperodon hydrochloride is soluble in alcohol, slightly soluble in acetone, ethyl acetate and water and insoluble in benzene and ether. Its 1 per cent aqueous solution is faintly acid to litmus.

**Actions and Uses.**—The actions and uses of diperodon hydrochloride are similar to those of cocaine, but the anesthesia lasts longer than that induced by corresponding doses of cocaine hydrochloride or procaine hydrochloride. Its toxicity by intravenous injection is about three times that of procaine hydrochloride and hence it should be injected only in small amounts. Diperodon hydrochloride is also available as a cream for topical use as a surface anesthetic and analgesic. It is useful for the relief of surface pain and irritation in abrasions of the skin and mucous membranes in nonoperable cases of hemorrhoids and following hemorrhoidectomy.

Extemporaneously prepared solutions of diperodon hydrochloride should be used promptly, since such solutions usually contain traces of alkali and are thereby subject to precipitation.

**Dosage.**—A 1 per cent solution may be applied to mucous membranes; a 0.5 per cent solution may be injected. (See the caution in the general statement on local anesthetics.) The cream is rubbed into the affected area, a second thin coating applied and they are covered with dressings within 10 or 15 minutes.

**THE WM. S. MERRELL COMPANY**

**Cream Diorthane Hydrochloride 1%:** 30 Gm. tubes and 480 Gm. jars.

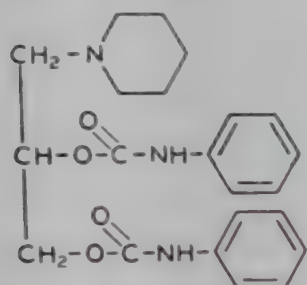
**Crystals Diorthane Hydrochloride:** 5 Gm. and 30 Gm. bottles for compounding use.

**Solution Diothane Hydrochloride 0.5% with Sodium Chloride 0.6%:** 5 cc. ampuls.

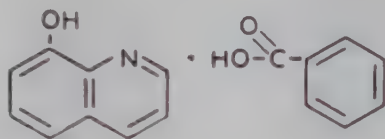
**Solution Diothane Hydrochloride 1%:** 60 cc. and 500 cc. bottles.  
A solution of diperonon hydrochloride in distilled water.

U. S. trademark 296,850.

**DIPERODON WITH HYDROXYQUINOLINE BENZOATE.**—Diothane with Oxyquinoline Benzoate (MERRELL).—3-(1-Piperidyl)-1,2-propanediol dicarbanilate and 8-hydroxyquinoline benzoate.—The structural formula of diperonon with hydroxyquinoline benzoate may be represented as follows:



Diperonon



8-Hydroxyquinoline benzoate

**Physical Properties.**—Diperonon with hydroxyquinoline benzoate is a yellowish, white, crystalline powder with a characteristic odor and taste due to the hydroxyquinoline benzoate. It is practically insoluble in water but very soluble in alcohol, benzene and ether.

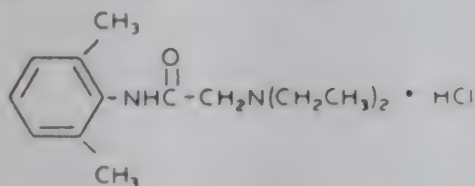
**Actions, Uses and Dosage.**—See the monograph on diperonon hydrochloride.

#### THE WM. S. MERRELL COMPANY

**Ointment Diothane with Oxyquinoline Benzoate:** 28.4 Gm. tubes and 454 Gm. jars. An ointment containing 1 per cent diperonon and 0.1 per cent oxyquinoline benzoate in an ointment base consisting of petrolatum, lanolin and mineral oil.

U. S. trademark 296,850.

**LIDOCAINE HYDROCHLORIDE.**—Xylocaine Hydrochloride (ASTRA).— $\alpha$ -Diethylamino-2,6-acetoxylidide hydrochloride.—Lidocaine hydrochloride is prepared in solution by the action of hydrochloric acid with lidocaine. The structural formula of lidocaine hydrochloride may be represented as follows:



**Physical Properties.**—The base lidocaine is a white, crystalline solid with a characteristic odor. It is very soluble in alcohol and

chloroform, freely soluble in benzene and ether and practically insoluble in water.

**Actions and Uses.**—Injection of lidocaine hydrochloride, a potent local anesthetic agent, produces more prompt, intense and extensive anesthesia than an equal concentration of procaine hydrochloride. Its anesthetic potency and the area of anesthesia are approximately twice those of procaine hydrochloride. At a concentration of 0.5 per cent, the toxicity of lidocaine hydrochloride in mice is the same as that of procaine hydrochloride, but as the concentration is increased, its toxicity exceeds that of procaine hydrochloride; at 1 per cent, it is 40 per cent greater; at 2 per cent, 50 per cent greater. It is compatible with epinephrine hydrochloride, with which it may be combined to delay absorption, prolong action and reduce its toxic effects. It is also used without epinephrine when vasopressor drugs are contraindicated. Systemic side reactions and local irritant effects are rare. Nausea and vomiting, muscular twitching and chilling have been observed.

Lidocaine hydrochloride is useful for infiltration and block anesthesia in dental as well as general surgical procedures. It is also effective topically for anesthesia of accessible mucous membranes and of the peritoneal cavity during surgery or instrumentation. The onset of mucosal anesthesia may be delayed as much as 5 minutes, and depending on the amount employed, the anesthesia persists of 30 minutes or more. It has been employed for continuous caudal, peridural and spinal (subarachnoid) anesthesia with promising results, but until its toxic potentialities have been compared with those of longer established agents such as procaine and tetracaine, it should be used only for the less hazardous low caudal anesthesia. Lidocaine hydrochloride provides adequate anesthesia by these routes with lower dosage.

**Dosage.**—Lidocaine hydrochloride is injected according to the type of local anesthesia to be induced. The maximum dose is the same as for procaine hydrochloride, i.e., 0.5 Gm. in 24 hours. When employed without epinephrine, as in patients who are hypersensitive to that substance, the maximum dose should be avoided and dosage reduced as much as possible.

Solutions of half the strength of those used in procaine anesthesia should provide equivalent anesthetic potency. It should be remembered that solutions containing more than 0.5 per cent of lidocaine hydrochloride are more toxic than similar concentrations of procaine hydrochloride.

For infiltration anesthesia the 0.5 per cent concentration with epinephrine hydrochloride 1:100,000 is ordinarily used, the volume injected depending on the extent of the area to be anesthetized. In minor surgery 2 to 50 cc. of this solution is usually adequate, but in major surgery, up to 100 cc. may be required. If larger amounts (up to 200 cc.) are injected, as in thoracoplasty, the solution should be 0.25 per cent. For block anesthesia a 1 or 2 per cent concentration with epinephrine hydrochloride 1:100,000 is used, depending on the site and structures concerned. The 2 per



cent concentration without epinephrine is suitable for block anesthesia of the digits. A 2 per cent solution with epinephrine 1:50,000 is used for certain odontologic procedures.

A 1 per cent solution is employed topically for mucosal anesthesia; it may be applied by means of cotton pledgets or applicators to the mucous membrane of the oral cavity or female urethra, to the peritoneum, or by injection into the male urethra.

#### ASTRA PHARMACEUTICAL PRODUCTS, INC.

**Solution Xylocaine Hydrochloride 0.5%:** 20 cc. and 50 cc. vials. A solution containing 5 mg. of lidocaine hydrochloride and 8 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

**Solution Xylocaine Hydrochloride 0.5% with Epinephrine Hydrochloride 1:100,000:** 20 cc. and 50 cc. vials. A solution containing 5 mg. of lidocaine hydrochloride, 0.01 mg. of epinephrine hydrochloride, and 8 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

**Solution Xylocaine Hydrochloride 1%:** 20 cc. and 50 cc. vials. A solution containing 10 mg. of lidocaine hydrochloride and 7 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

**Solution Xylocaine Hydrochloride 1% with Epinephrine Hydrochloride 1:100,000:** 20 cc. and 50 cc. vials. A solution containing 10 mg. of lidocaine hydrochloride, 0.01 mg. of epinephrine hydrochloride, and 6 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

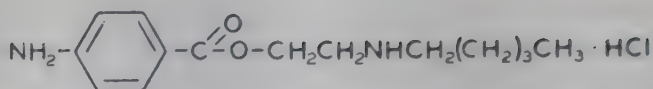
**Solution Xylocaine Hydrochloride 2%:** 20 cc. and 50 cc. vials and 1.8 cc. cartridges. A solution containing 20 mg. of lidocaine hydrochloride and 6 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

**Solution Xylocaine Hydrochloride 2% with Epinephrine Hydrochloride 1:100,000:** 20 cc. and 50 cc. vials and 1.8 cc. cartridges. A solution containing 20 mg. of lidocaine hydrochloride, 0.01 mg. of epinephrine hydrochloride, and 6 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

**Solution Xylocaine Hydrochloride 2% with Epinephrine Hydrochloride 1:50,000:** 50 cc. vials and 1.8 cc. cartridges. A solution containing 20 mg. of lidocaine hydrochloride, 0.02 mg. of epinephrine hydrochloride, and 6 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

U. S. patent 2,441,498. U. S. trademark 534,232.

**NAEPAIN HYDROCHLORIDE.**—Amylsine Hydrochloride (Novocol).—2-Amylaminoethyl *p*-aminobenzoate hydrochloride.—The structural formula of naepaine hydrochloride may be represented as follows:



**Physical Properties.**—Naepaine hydrochloride is a fine, white, odorless powder which, when applied to the tongue, produces a bitter taste followed by a sense of numbness. It is soluble in water, sparingly soluble in alcohol and insoluble in benzene, chloroform and ether. The free base (m.p.  $65^\circ$ ) separates as a solid from solutions of the hydrochloride on the addition of sodium hydroxide or carbonate T.S. but not with 5 per cent sodium bicarbonate. The hydrochloride is dimorphic. The form which crystallizes from amyl alcohol melts at  $176^\circ$ , while the one crystallized from water melts at  $153.5^\circ$ . Aqueous solutions are acid to litmus.

**Actions and Uses.**—The actions of naepaine hydrochloride resemble those of cocaine hydrochloride, but the solution does not cause mydriasis when dropped into the eye. Its use should be restricted to the production of corneal anesthesia in cases in which mydriasis is not desired. The toxicity varies widely with the species and with the mode of administration. The anesthesia is induced promptly with little smarting and the drug does not increase intraocular tension.

**Dosage.**—A 2 per cent or 4 per cent solution is used in ophthalmology when mydriasis is not desired, 1 or 2 drops usually being sufficient.

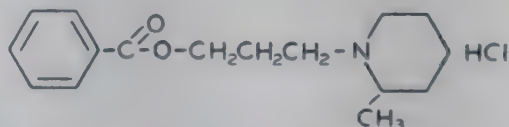
NOVOCOL CHEMICAL MFG. COMPANY, INC.

**Powder Amylsine Hydrochloride:** 5 Gm. vials and 28.3 Gm. bottles.

**Solution Amylsine Hydrochloride 4%:** 30 cc. bottles.

U. S. patent 2,139,818 (Dec. 13, 1938; expires 1955). U. S. trademark 404,009.

**PIPEROCAINE HYDROCHLORIDE-U.S.P.**—**Metycaine Hydrochloride (LILLY).**—3-(2-Methyl-1-piperidyl)propyl benzoate hydrochloride.—“Piperocaine Hydrochloride, dried at  $105^\circ$  for 3 hours, contains not less than 98 per cent of  $\text{C}_{16}\text{H}_{18}\text{NO}_2 \cdot \text{HCl}$ .” U.S.P. The structural formula of piperocaine hydrochloride may be represented as follows:



**Physical Properties.**—Piperocaine hydrochloride occurs as small, white crystals or as a white, crystalline powder. It is odorless and is stable in air. When piperocaine hydrochloride is placed on the tongue it exhibits a slightly bitter taste followed by a sense of numbness. A solution of piperocaine hydrochloride (1 in 10) is acid to litmus paper. One gram of piperocaine hydrochloride dissolves in 1.5 cc. of water and in 4.5 cc. of alcohol. It is readily soluble in chloroform but almost insoluble in ether and in fixed oils.



**Actions and Uses.**—Piperocaine hydrochloride is a local anesthetic which produces prompt anesthesia either by subcutaneous injection or topical application to mucous membranes and similar surfaces. Pharmacologic studies on animals indicate that its toxicity following subcutaneous injection is lower than that of cocaine and comparable to that of procaine; injected intravenously, it is approximately three times as toxic as procaine. It is considered the approximate equivalent of procaine for spinal anesthesia. Piperocaine hydrochloride is more controllable when weighted with glucose. A 3 per cent solution weighted with 5 per cent dextrose is used for saddle block and minimal spinal anesthesia.

**Dosage.**—For application to the eye piperocaine hydrochloride is used in 2 to 4 per cent solutions; for nose and throat, 2 to 10 per cent; for the urethra, 1 to 4 per cent; for infiltrative anesthesia, 0.5 to 1 per cent; for nerve block, 1 to 2 per cent; for spinal anesthesia, 1.5 to 5 per cent, the maximum quantity of drug being 0.75 mg. per pound of body weight and the absolute maximum being 150 mg. For saddle block and minimal spinal anesthesia, a single injection of 1 cc. of a 3 per cent solution (30 mg.) weighted with 5 per cent dextrose is considered sufficient to provide anesthesia for 75 minutes. For cesarean section or other low or mid-abdominal surgery, 1.5 cc. of 3 per cent piperocaine hydrochloride (45 mg.) in 5 per cent dextrose may be more desirable. (See caution in the general statement on local anesthetics.)

#### ELI LILLY & COMPANY

**Ointment Metycaine Hydrochloride 5%:** 3.89 Gm. tubes. An ointment containing 50 mg. of piperocaine hydrochloride in a base consisting of white petrolatum with white wax and wool fat.

**Ophthalmic Ointment Metycaine Hydrochloride 4%:** 14 Gm. tubes. An ointment containing 40 mg. of piperocaine hydrochloride in a base consisting of liquid petrolatum, wool fat and with small amounts of paraffin, white petrolatum and ceresin.

**Powder Metycaine Hydrochloride:** 15 Gm. and 120 Gm. bottles.

**Solution Metycaine Hydrochloride 1.5%:** 200 cc. ampul-bottles. A Ringer's solution containing 15 mg. of piperocaine hydrochloride in each cubic centimeter. For caudal anesthesia.

**Solution Metycaine Hydrochloride 3% and Dextrose 5%:** 1.5 cc. ampuls. A solution containing 30 mg. of piperocaine hydrochloride and 50 mg. of dextrose in each cubic centimeter.

**Solution Metycaine Hydrochloride 20%:** 5 cc. ampuls. A solution containing 0.2 Gm. of piperocaine hydrochloride in each cubic centimeter. To be used for infiltration and regional anesthesia. The solution must be diluted before use.

**Solution Metycaine Hydrochloride:** 30 cc. vials. A Ringer's solution containing 20 mg. of piperocaine hydrochloride in each cubic centimeter.

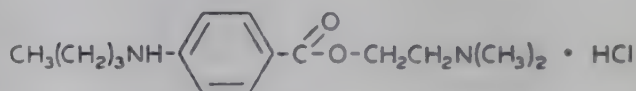


**Solution Metycaine Hydrochloride:** 5 cc. ampuls. A Ringer's solution containing 15 mg. of piperocaine hydrochloride in each cubic centimeter. For spinal anesthesia.

**Tablets Metycaine Hydrochloride:** 0.15 Gm.

U. S. trademark 305,894.

**TETRACAINE HYDROCHLORIDE-U.S.P.—Pontocaine Hydrochloride** (WINTHROP-STEARNs).—2-Dimethylaminoethyl *p*-butylaminobenzoate hydrochloride.—“Tetracaine Hydrochloride, dried over sulfuric acid for 4 hours, contains not less than 98.5 per cent  $C_{15}H_{24}N_2O_2 \cdot HCl$ .” *U.S.P.* The base of tetracaine hydrochloride differs from procaine base in that one of the hydrogens of the *p*-amino group is replaced by a butyl group, and the two ethyl groups of procaine are replaced by two methyl groups. The structural formula of tetracaine hydrochloride may be represented as follows:



**Actions and Uses.**—Tetracaine hydrochloride is a local anesthetic with actions similar to those of procaine hydrochloride, but when applied to mucous membranes it is effective in lower concentrations. (See caution in the general statement on local anesthetics.) It is used for surface anesthesia in the eye, nose and throat, for prolonged spinal anesthesia and for continuous caudal analgesia.

**Dosage.**—Solution of tetracaine hydrochloride, 0.5 per cent is used in the eye; a 2 per cent solution is applied to the nose and throat. A 0.5 per cent solution is injected for spinal anesthesia, the dose being from 2 to 4 cc. (from 10 to 20 mg. of the salt). A total of 20 mg. is considered the maximum safe dose for spinal injection.

For continuous caudal analgesia an initial skin wheal is raised with the local anesthetic and the underlying tissues infiltrated so that the needle may be inserted into the sacral canal without excessive discomfort to the patient. Thirty cubic centimeters tetracaine hydrochloride 0.15 per cent solution is injected. Signs of fullness in one or both legs, progressive loss of painful sensations and relief of abdominal uterine cramps will occur in 5 to 15 minutes. Supplementary injections depend on the individual patient. Usually from 10 to 20 cc. of tetracaine hydrochloride 0.15 per cent solution injected at intervals of from 40 to 90 minutes are sufficient to keep the patient comfortable during the entire course of labor. In many cases 100 cc. of the 0.15 per cent solution is sufficient for the management of labor, delivery and repairs.

Solutions of tetracaine hydrochloride, made hyperbaric with 6 per cent dextrose, are employed in a concentration of 0.2 per cent for the production of low spinal anesthesia by the saddle block technic in obstetric and perineal surgery and in a concentration of 0.3 per cent for low, median or high spinal anesthesia in general surgery; the single total dosage employed for such procedures should not exceed 6 mg.

**WINTHROP-STEARNs, INC.**

**Ophthalmic Ointment Pontocaine Base:** An ointment containing 0.5 per cent of tetracaine base, the free base of tetracaine hydrochloride, dissolved in white petrolatum.

**Pontocaine Hydrochloride "Niphanoid":** Ampuls containing 10 mg., 15 mg. or 20 mg. of tetracaine hydrochloride. For spinal anesthesia.

**Solution Pontocaine Hydrochloride:** 100 cc. bottles. An isotonic solution containing 1.5 mg. of tetracaine hydrochloride in each cubic centimeter. For caudal anesthesia.

**Solution Pontocaine Hydrochloride 0.2% with Dextrose 6%:** 2 cc. ampuls. A hyperbaric solution containing 2 mg. of tetracaine hydrochloride in each cubic centimeter. For saddle block anesthesia.

**Solution Pontocaine Hydrochloride 0.3% with Dextrose 6%:** 5 cc. ampuls. A hyperbaric solution containing 3 mg. of tetracaine hydrochloride in each cubic centimeter. For spinal anesthesia.

**Solution Pontocaine Hydrochloride 0.5%:** 15 cc. and 60 cc. bottles. Preserved with 0.4 per cent chlorobutanol.

**Solution Pontocaine Hydrochloride 1%:** 2 cc. ampuls. A solution containing 10 mg. of tetracaine hydrochloride, 6.6 mg. of sodium chloride, and 2 mg. of acetone sodium bisulfite in each cubic centimeter.

**Solution Pontocaine Hydrochloride 2%:** 30 cc. and 120 cc. bottles. Preserved with 0.4 per cent chlorobutanol. Tinted with methylene blue to prevent accidental use for injection.

**Tablets Pontocaine Hydrochloride:** 0.1 Gm. Each tablet contains 0.1 Gm. of tetracaine hydrochloride, 5 mg. of boric acid, and not more than 0.5 mg. of acetone sodium bisulfite. To be used only for preparing solutions for surface anesthesia (not for injection) in rhinolaryngology, ophthalmology and dentistry.

U. S. trademark 282,418.

## 4

# Local Anti-Infectives

The drugs included in this chapter are antibacterials, fungicides and antiprotozoan agents. Agents of these classes that are administered internally (orally or parenterally), though employed for their local action, are described in the chapter on systemic anti-infectives. The antibacterials include disinfectants (the names germicide and bactericide are synonyms), antiseptics (bacteriostatic or growth-preventing substances) and antibiotics. No sharp distinction can be drawn between disinfectants and antiseptics. Antibiotics are effective as disinfectants and/or antiseptics. The term "antibiotic" here denotes chemical compounds, derived from or produced by living organisms, which are capable in small concentrations of inhibiting the life processes of micro-organisms.

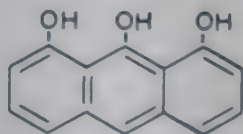
The ideal disinfectant or antiseptic would possess the following assets: High coefficient of disinfection, stability, solubility and penetrability even in the presence of organic matter. It would be highly bacteriostatic, but nontoxic, noncorrosive and nonbleaching. Antiseptics and disinfectants should possess nonspecific action on micro-organisms.

Criteria for the evaluation of disinfectants and antiseptics are not well established. The incorporation of "inactivators" in both in vitro and in vivo tests of the bactericidal and bacteriostatic properties of antibacterial agents will undoubtedly aid in establishing their efficacies. Unfortunately, adequate neutralizers for all of the active compounds included in antibacterial agents have not yet been discovered.

For the Council's requirements for the acceptance of disinfectants and antiseptics, see section in the rules on Evaluation of Certain Products.

## ANTHRACENE DERIVATIVES

**ANTHRALIN-N.F.**—1,8,9-Anthratriol.—"Anthralin, dried over sulfuric acid for 4 hours, contains not less than 95 per cent and not more than 101 per cent of  $C_{14}H_{10}O_3$ ." *N.F.* The structural formula of anthralin may be represented as follows:



**Physical Properties.**—Anthralin occurs as an odorless, tasteless, crystalline, yellowish brown powder. When suspended in water and



filtered, the filtrate is neutral to litmus paper. It is soluble in chloroform, in acetone and in benzene. It is soluble in solutions of alkali hydroxides and slightly soluble in alcohol, in ether and in glacial acetic acid. It is insoluble in water.

**Actions and Uses.**—Anthralin is recommended as a substitute for chrysarobin in the treatment of psoriasis because it has less tendency to produce conjunctivitis when used about the face and scalp and less tendency to cause dermatitis or discoloration of the skin. The preparation has also been recommended in the treatment of chronic dermatomycosis and for stimulating action in chronic dermatoses.

**Dosage.**—Anthralin is employed in concentrations of 0.1 per cent to 1.0 per cent in ointments or creams. It is always well to begin with lower concentrations because anthralin tends to irritate the skin.

#### ABBOTT LABORATORIES

**Ointment Anthralin:** 0.1 per cent, 0.25 per cent, 0.5 per cent or 1 per cent anthralin in a petrolatum base.

## ANTIBIOTICS

**TYROTHRINICIN-U.S.P.**—Soluthricin (SHARP & DOHME).—"Tyrothricin is an anti-bacterial substance produced by the growth of *Bacillus brevis* Dubos (Fam. *Bacteriaceae*). It consists principally of gramicidin and tyrocidine, the tyrocidine usually being present as the hydrochloride.

Tyrothricin has a potency of not less than 90 per cent of the U.S.P. Tyrothricin Reference Standard." U.S.P.

**Physical Properties.**—Tyrothricin occurs as a white to buff-colored powder. It is soluble in alcohol, acetone and dioxane; insoluble in water, chloroform and ether. It is resistant to the action of pepsin and trypsin. Heat and exposure to proteolytic enzymes render it insoluble in neutral buffer solutions.

**Actions and Uses.**—Tyrothricin consists of at least two substances, gramicidin and tyrocidine, the former being the more active component. It is probable that some of the earlier reports supposedly based on the use of gramicidin were actually concerned with this mixture. Among the organisms that are susceptible are species of pneumococci, streptococci and staphylococci. Tyrothricin inhibits enzymatic action, retards growth and causes lysis of susceptible bacteria.

Tyrothricin is ineffective when administered orally and ineffective and dangerous when given intravenously.

It may be used with caution in body cavities as long as there is no direct connection with the blood stream. But in no instance should proper surgical treatment be omitted. It has been of value in the treatment of superficial indolent ulcers where the predominating organism is gram-positive, and in mastoiditis, empyema and some other wound infections. Its field of usefulness is limited and it exerts no effect unless it comes in direct contact with the organisms. Thus it may not be effective in the presence of deep-

seated infections. Body fluids such as saliva, urine and serum inhibit action slightly, whereas substances from gram-negative organisms are decidedly inhibiting.

Indiscriminate use of tyrothricin solutions for irrigation of the paranasal sinuses or other cavities close to the subarachnoid space following surgery should be avoided because of the danger of chemical meningitis.

**Dosage.**—Tyrothricin must be applied locally, *not intravenously or by mouth*. It is administered after dilution with sterile distilled water to form an isotonic solution which yields 500 mcg. of the drug per cubic centimeter. This concentration is usually effective. Higher concentrations may be used if indicated, but may irritate the tissues.

#### PARKE, DAVIS & COMPANY

**Solution Tyrothricin 2%:** 10 cc. and 50 cc. vials. A 92 per cent alcoholic solution containing 20 mg. of tyrothricin in each cubic centimeter.

#### S. B. PENICK & COMPANY

**Solution Tyrothricin 4%:** 200 cc. and 500 cc. vials. A 23 per cent alcoholic solution containing 40 mg. of tyrothricin in each cubic centimeter.

**Tyrothricin:** Bulk. 100 Gm., 500 Gm. and 1,000 Gm. glass jars.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

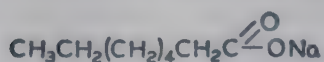
**Solution Soluthricin 0.05%:** 240 cc. bottles. A solution in 1 per cent alcohol, propylene glycol and water containing 0.5 mg. each of tyrothricin and cetyldimethylethylammonium bromide in each cubic centimeter.

**Solution Soluthricin (Concentrate) 2.5%:** 10 cc. and 20 cc. vials. A solution in 50 per cent alcohol and propylene glycol containing 25 mg. each of tyrothricin and cetyldimethylethylammonium bromide in each cubic centimeter.

U. S. trademark 421,710.

## ANTIFUNGAL AGENTS

**CAPRYLIC COMPOUND.**—Naprylate (STRASENBURG).—A mixture of 10 per cent sodium caprylate and 5 per cent zinc caprylate. Their structural formulas may be represented as follows:



Sodium caprylate



Zinc caprylate

**Physical Properties.**—Caprylic compound is a fine, white powder with a characteristic odor. It is partially soluble in water and is slightly soluble in alcohol.

**Actions and Uses.**—Caprylic compound has been found useful for



the prevention and treatment of dermatophytosis pedis and for the control of other superficial fungous infections of the skin and accessible mucous membranes. Applied topically it is effective against infection due to trichophytons, microsporons and *Monilia albicans*. Moderate concentrations of caprylic acid salts do not produce irritation or sensitization of the skin and are not subject to absorption from the skin or mucous membranes.

**Dosage.**—Caprylic compound powder or ointment is topically applied to the skin after the affected part has been thoroughly cleaned. The two may be used concomitantly, the powder being applied during the day and the ointment during the night. The powder may be dusted into the shoes and stockings for the control of susceptible fungous infections involving the feet. The ointment is also used in the treatment of monilial stomatitis or thrush.

For the control of monilial vulvovaginitis caprylic compound is applied in the form of powder by insufflation and in the form of an ointment by means of a vaginal applicator. A 5 per cent solution of sodium caprylate (prepared by diluting a 20 per cent solution with 3 parts of water) may be used in stubborn cases for preliminary cleansing of the vagina prior to application of caprylic compound. Approximately 30 cc. of a 20 per cent solution of sodium caprylate may be added to 1000 cc. of lukewarm water as a cleansing douche during therapy with caprylic compound. During pregnancy, this type of treatment should not be used after the seventh month.

#### R. J. STRASENBURGH COMPANY

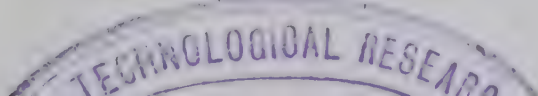
**Ointment Naprylate:** 21.25 Gm. tubes and 454 Gm. jars. An ointment containing 0.1 Gm. of sodium caprylate and 50 mg. of zinc caprylate in each gram.

**Powder Naprylate:** 35.43 Gm. flexible plastic bottles. A powder containing 0.1 Gm. of sodium caprylate and 50 mg. of zinc caprylate in each gram.

**COPARAFFINATE.**—*Iso-Par* (MEDICAL CHEM.).—A mixture of water-insoluble isoparaffinic acids partially neutralized with isoocetyl hydroxybenzylalkyl amines. The water-insoluble isoparaffinic acids are obtained by oxidation of petroleum hydrocarbons by the passage of a current of oxygen under pressure, at an elevated temperature and in the presence of a metallic catalyst. The water-insoluble monocarboxylic and dicarboxylic acids with 6 to 16 carbon atoms are separated and purified by fractional distillation. The hydroxybenzylalkyl amines are combined with the isoparaffinic acids directly or in a suitable solvent. The latter is then removed by distillation.

**Physical Properties.**—Coparaffinate is a viscous, dark brown, oily liquid with the characteristic odor of burnt petroleum. It is immiscible with water, but freely miscible with alcohol and volatile and fixed oils. Its specific gravity is between 0.970 and 0.980.

**Actions and Uses.**—Coparaffinate ointment is for external use only. Thick or tight bandaging may cause irritation. Coparaffinate





is of value in the treatment of pruritus ani and vaginae, mycotic infections of the hands and feet, eczemas of the ear and certain dermatologic manifestations of allergy. This ointment is stimulating, lowers the levels of irritability of the skin and is in varying degrees bactericidal and fungicidal.

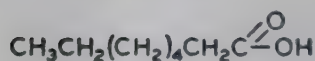
**Dosage.**—It should be applied with a rubber finger stall, a small wad of absorbent cotton or gauze or other convenient applicator, since it possesses an odor which may be objectionable if it persists on the fingers. The first applications may cause a temporary burning sensation. The ointment should be applied to the affected area in the evening before retiring and again in the morning; if necessary, it may be applied more frequently. The majority of cases respond within 3 to 5 days, but others may require up to 2 weeks. If relief is not obtained by that time, some other form of treatment should be substituted.

#### MEDICAL CHEMICALS, INC.

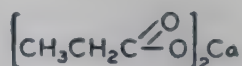
**Ointment Iso-Par:** 14 Gm., 28.5 Gm., 114 Gm. and 454 Gm. jars. An ointment containing 17 per cent coparaffinate and 4 per cent titanium dioxide in a base consisting of beeswax, cetyl alcohol, lanolin and petrolatum.

U. S. patent 2,262,720. U. S. trademark 365,069.

**PROPIONATE-CAPRYLATE MIXTURES.**—Preparations in which the formulation is varied with respect to both the ingredients and their concentrations according to the dosage form. The active ingredients are chosen from the following: calcium propionate, caprylic acid, propionic acid, sodium propionate-N.F., zinc caprylate and zinc propionate. Their structural formulas may be represented as follows:



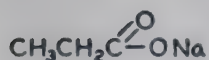
Caprylic acid



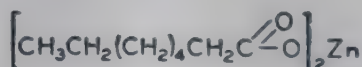
Calcium propionate



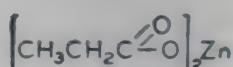
Propionic acid



Sodium propionate



Zinc caprylate



Zinc propionate

**Actions and Uses.**—Propionate-caprylate mixtures are used against superficial fungous infections, especially dermatophytosis of the feet, hands and groin.

**Dosage.**—Cleanse the affected parts and apply morning and night.

#### WYETH LABORATORIES, INC.

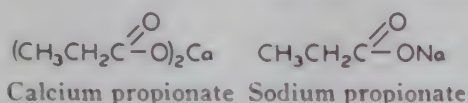
**Ointment Sopronol Propionate-Caprylates Compound:** 30 Gm. and 120 Gm. tubes. A water-soluble ointment containing 12.3 per cent sodium propionate, 2.7 per cent propionic acid, 10 per cent sodium caprylate, 5 per cent zinc caprylate and 0.1 per cent dioctyl sodium sulfosuccinate.

**Powder Sopronol Propionates-Caprylate Compound:** 60 Gm. and 150 Gm. canisters. A dusting powder containing 15 per cent calcium propionate, 5 per cent zinc propionate, 5 per cent zinc caprylate and 0.25 per cent propionic acid in a talc base.

**Solution Sopronol Propionate-Caprylate Compound:** 60 cc. bottles. A dilute *n*-propyl alcohol solution containing 12.3 per cent sodium propionate, 2.7 per cent propionic acid, 10 per cent sodium caprylate, and 0.1 per cent dioctyl sodium sulfosuccinate.

Licensed under U. S. patents 2,217,905 and 2,466,663; U. S. trademark 410,284.

**PROPIONATE COMPOUND.—Propion Gel (WYETH).—**A mixture of calcium propionate 10 per cent and sodium propionate 10 per cent, marketed in the form of a water-miscible jelly. The structural formulas of the active ingredients may be represented as follows:



**Actions and Uses.**—Propionate compound in the form of jelly is used for local application in the treatment of vulvovaginal moniliasis. Until more evidence becomes available, it is not recommended for other mycotic infections of the vulva or vagina, despite the fact that propionic acid compounds have been shown to be effective against a variety of fungous infections of the skin. It should be kept in mind that *Monilia* are occasionally found in the vaginal secretions of apparently normal women; when they are associated with *Trichomonas* infection, treatment of the latter sometimes clears up the symptoms. The relationship between these two organisms in vulvovaginitis is not yet completely understood.

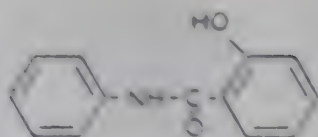
**Dosage.**—Approximately 6 cc. of a jelly containing the propionate compound applied to the upper part of the vagina twice daily (morning and night) by means of an applicator. A single plain water douche is recommended before the first application, but douches are not permitted during treatment. A small amount of the jelly should be externally applied to the vulva. When there is considerable excoriation, the first two or three external applications should be made with the jelly diluted with an equal volume of water. To determine cure, culture for *Monilia* may be taken two days after therapy has been discontinued. Vaginal applicators should not be used after the seventh month of pregnancy.

WYETH LABORATORIES, INC.

**Propion Gel:** 95 Gm. tubes with vaginal applicator. A water-miscible jelly containing 0.1 Gm. each of calcium propionate and sodium propionate in each gram.

U. S. trademark 434,356.

**SALICYLANILIDE-N.F.—Ansadol (RORER).—Salinidol (DOAK).—**The structural formula of salicylanilide may be represented as follows:



**Physical Properties.**—Salicylanilide occurs as odorless, white or slightly pink crystals which are stable in air. It is freely soluble in alcohol, in ether, in chloroform and in benzene. It is slightly soluble in water.

**Actions and Uses.**—Salicylanilide is an antifungal agent useful externally in the treatment of tinea capitis due to *Microsporon audouinii*. Against that organism, in vitro, salicylanilide has approximately eight times the fungistatic power of undecylenic acid, but concentrations above 5 per cent irritate the skin. Because of its potential irritant effects on the skin, the use of salicylanilide should be restricted to ringworm of the scalp.

**Dosage.**—Salicylanilide is applied topically in concentrations of 4.5 to 5 per cent, usually in the form of an ointment, either alone or in conjunction with less irritant fungistatic agents. The hair should be clipped from the affected and adjacent areas of the scalp prior to treatment and every 2 weeks thereafter during treatment. The clippings should be burned and a shampoo given after each clipping. Suitable preparations of the agent should be rubbed into the affected regions once or twice daily, 6 days each week. About 50 single daily applications (8 weeks) are usually required to completely eradicate infection.

#### DOAK PHARMACAL COMPANY, INC.

Ointment Salinidol 5%: 113.4 Gm., 453.6 Gm. and 2.27 Kg. jars. An ointment containing 50 mg. of salicylanilide in each gram.

U. S. trademark 502,126.

#### WILLIAM H. RORER, INC.

Ointment Ansadol 4.5 %: 113.4 Gm. and 453.6 Gm. jars. An ointment containing 45 mg. of salicylanilide in each gram.

**SODIUM CAPRYLATE.**—The sodium salt of caprylic acid.—The structural formula of sodium caprylate may be represented as follows:



**Physical Properties.**—Sodium caprylate forms cream-colored granules. It is freely soluble in water and sparingly soluble in alcohol.

**Actions and Uses.**—Sodium caprylate is applied topically in the treatment of superficial fungous infections of the skin due to trichophytons, microsporon and *Monilia albicans*. Repeated daily use has not produced irritation or sensitization of the skin.

**Dosage.**—Sodium caprylate is employed in the form of solution.



powder or ointment, in concentrations of 10 to 20 per cent. A solution of 20 per cent is topically applied to the affected skin with a cotton applicator or by other suitable means after thorough cleansing of the involved parts.

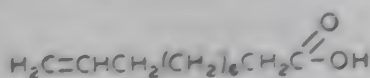
#### CHEMO PURG MANUFACTURING CORPORATION

Powder Sodium Caprylate: Bulk; for manufacturing use.

#### R. J. STRASBURGH COMPANY

Solution Sodium Caprylate: 60 cc., 480 cc. and 3.83 liter bottles. An aqueous solution containing 0.2 Gm. of sodium caprylate in each cubic centimeter.

**UNDECYLENIC ACID-N.F.**—"Undecylenic acid contains not less than 95 per cent of  $C_{11}H_{20}O_2$ ." *N.F.* The structural formula of undecylenic acid may be represented as follows:



**Physical Properties.**—Undecylenic acid occurs as a yellow liquid having a characteristic odor. It is almost insoluble in water but is miscible with alcohol, chloroform, ether and benzene and with fixed and volatile oils.

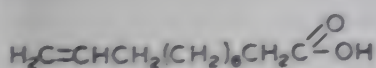
**Actions and Uses.**—Undecylenic acid is one of the more potent fatty acids employed topically as a fungistatic agent in the treatment of superficial fungus infections. Local application occasionally produces irritation and internal use for the treatment of psoriasis or other skin conditions is not established.

**Dosage.**—Undecylenic acid is applied topically in the form of a solution or emulsion in concentrations not to exceed 10 per cent. This strength may produce burning when applied to mucous membranes; it should therefore be diluted to a 1 per cent concentration for irrigation of these structures.

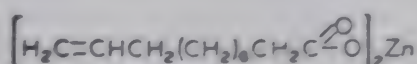
#### WALLACE & TIERNAN, INC.

Desenex Solution Undecylenic Acid 10%: 59 cc. and 473 cc. bottles. A solution containing 92 mg. of undecylenic acid in each cubic centimeter.

**ZINCUNDECATE.**—Undesol (VELTEX).—A preparation containing as its active ingredients undecylenic acid-N.F. and zinc undecylenate-N.F. Their structural formulas may be represented as follows:



Undecylenic acid



Zinc undecylenate

**Actions and Uses.**—Zincundecate is used for superficial dermatomycosis, epidermatophytosis including epidermatosis inguinale,

tinea pedis, otomycosis, moniliasis, tinea corporis and tinea versicolor.

**Dosage.**—Apply twice daily, preferably using the ointment at night, and with ambulatory patients, the powder during the day.

#### VELTEX COMPANY

**Ointment Undesol:** 30 Gm., 60 Gm., 454 Gm. and 2270 Gm. jars. An ointment containing 0.2 Gm. of zinc undecylenate and 50 mg. of undecylenic acid in each gram.

**Powder Undesol:** 90 Gm. containers and 454 Gm. jars. A fungistatic powder containing 20 per cent zinc undecylenate and 2 per cent undecylenic acid.

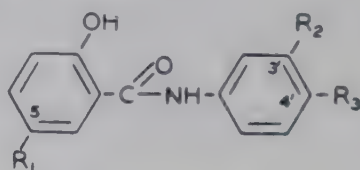
#### WALLACE & TIERNAN, INC.

**Desenex Ointment Zincundecate:** 28.3 Gm. tubes and 454 Gm. jars. A fungistatic ointment containing 20 per cent zinc undecylenate and 5 per cent undecylenic acid. It is buffered at pH 6.5 by the addition of triethanolamine, in a water-miscible base, q. s.

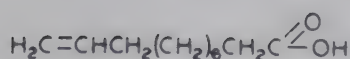
**Desenex Powder Zincundecate:** 42.5 Gm. sifter containers and 454 Gm. containers. A fungistatic powder containing 20 per cent zinc undecylenate and 2 per cent undecylenic acid.

U. S. patents 2,510,946 and 2,511,032. U. S. trademark 413,804.

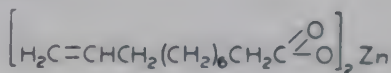
**ZINCHLORUNDESAL.**—**Salundek (New)** (WALLACE & TIERNAN).—A mixture of salicylanilide-N.F., 5-chlorosalicylanilide, 5,3'-dichlorosalicylanilide, and 5,4'-dichlorosalicylanilide with undecylenic acid-N.F. and zinc undecylenate-N.F. Their structural formulas may be represented as follows:



Salicylanilide



Undecylenic acid



Zinc undecylenate

**Actions and Uses.**—Zinchlorundesal is effective topically in the treatment of tinea capitis caused by *Microsporon audouini*. Its use generally should be restricted to this purpose because of its potential irritant effects, although zinchlorundesal is also effective in the treatment of superficial dermatomycoses. If a cure is not obtained in 4 months, the patient should be referred for consideration of x-ray treatment.

In zinchlorundesal the irritant potentialities of the salicylanilides are minimized because lower concentrations are used, but, nevertheless, they are highly effective when combined with one another and with the relatively nonirritating undecylenic acid components.

The fungistatic potency of salicylanilide in vitro is approximately eight times that of undecylenic acid against *M. audouini*, and the chlorosalicylanilides are 5 to 150 times as active as salicylanilide in inhibiting the growth of this micro-organism.

**Dosage.**—Zinchlorundesal is applied topically in the form of an ointment containing the stated proportions of the active ingredients. It is rubbed on the affected and adjacent areas twice daily.

WALLACE & TIERNAN, INC.

**Ointment Salundek (New):** 28.3 Gm. tubes and 454 Gm. jars. An ointment containing 30 mg. of salicylanilide, 20 mg. of 5-chlorosalicylanilide, 10 mg. each of 5,3'- and 5,4'-dichlorosalicylanilides, 20 mg. of undecylenic acid and 100 mg. of zinc undecylenate in each gram.

U. S. trademark 572,472.

## PHENOL DERIVATIVES

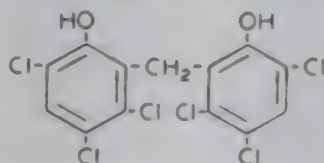
Phenol derivatives include the cresols and the diphenols. Cresols are phenols in which one of the hydrogen atoms has been replaced by a methyl group. The official cresol is a mixture of the three isomers, *ortho*-, *meta*-, and *para*-cresol. They are only moderately soluble in water, about 1:50, but are readily emulsified in the presence of soap and alkalis; however, excess soap and alkali diminish their germicidal efficiency.

The antibacterial specificities of the cresols closely parallel those of phenol. Cresols are highly effective against acid-fast bacteria, but have limited virucidal value; they are not sporicidal. In contrast to other disinfectants, the cresol compounds retain their germicidal properties remarkably well in the presence of organic matter.

The toxicity and local actions of the cresols, as of other phenols, may be diminished by "masking" the active OH group by the formation of esters.

Diphenols, such as hexachlorophene, are derivatives of diphenyl, diphenylmethane and diphenylsulfide. These substances are weakly acidic and it is believed that when combined with excess alkali, as in soap, only one of the two phenolic groups is neutralized, while the other retains antibacterial properties.

**HEXACHLOROPHENE.** — Gamophen (ETHICON). — Hex-O-San (RETORT). — pHisoHex (WINTHROP-STEARN'S). — Surgi-Cen (CENTRAL). — 2,2'-Methylenebis-(3,4,6-trichlorophenol). — 2,2'-Dihydroxy-3,5,6,3',5',6'-hexachlorodiphenylmethane. — The structural formula of hexachlorophene may be represented as follows:





**Physical Properties.**—Hexachlorophene is an odorless (or with a slight, phenolic odor), white to light tan, crystalline powder, which melts between 161 and 167°. It is freely soluble in acetone, alcohol and ether, soluble in chloroform and insoluble in water.

**Actions and Uses.**—Hexachlorophene is incorporated in soaps, detergent creams, oils and other vehicles for topical application to reduce the numbers and to inhibit the metabolism of micro-organisms which occur naturally and pathogenically in the skin bacterial flora.

Residual amounts of hexachlorophene, which are adsorbed on the skin, maintain a reduction in numbers of bacteria. Optimum results are obtained only with regular daily application of the agent to the skin surface; substitution of other cleansing agents, including water, removes the adsorbed hexachlorophene with a resultant rapid increase in numbers and metabolism of micro-organisms. Application of alcohol or other organic solvents to the skin should be avoided. The activity of hexachlorophene, like that of many antibacterial agents, is considerably reduced by blood serum and other organic matter.

Hexachlorophene is effective against gram-positive bacteria; the gram-negative organisms are much more resistant to its action. No evidence is presently available concerning its efficacy against acid-fast bacteria, fungi, bacterial spores, viruses or spirochetes. Irritant and toxic effects of hexachlorophene on the skin surface, even after long-continued daily use, have been infrequently reported. Data have not been presented on the possibility of acquired resistance of the skin bacterial flora following prolonged use of hexachlorophene.

Products containing hexachlorophene are used for preoperative scrubbing, and preoperative and postoperative preparation of patients' skin. When used continually hexachlorophene is also an effective prophylactic agent in decreasing the incidence and severity of pyogenic skin infections including carbuncles, furuncles, miliaria, ammoniacal dermatitis, impetigo and seborrheic dermatitis ("cradle cap"). Neither hexachlorophene nor any other chemical agent should be relied on as a substitute for mechanical cleansing of the skin.

**Dosage.**—For use as an antibacterial agent hexachlorophene may be incorporated in a number of vehicles, i.e., soap, detergents, creams and oils. Concentrations of 2 to 3 per cent in bar and liquid soaps (based on the amount of anhydrous soap present) and in detergent preparations, and concentrations of 0.5 to 1 per cent in products which are applied to the skin undiluted are efficacious in reducing the number of micro-organisms inherent in the skin bacterial flora; maintenance of reduced numbers depends upon regular daily applications of the agent to the treated area. Concentrations in excess of 3 per cent have not yet been shown to be more effective.

THE BOWMAN BROS. DRUG COMPANY

Surgical Soap Hexachlorophene: 473 cc. and 3.78 liter bottles

A soap containing 0.72 per cent hexachlorophene (2 per cent anhydrous soap basis).

#### CENTRAL CHEMICAL COMPANY, INC.

Liquid Soap Surgi-Cen: 3.78, 18.9, 56.7, 113.4, 132.4 and 208.1 liter containers. A soap containing 1 per cent hexachlorophene (2.5 per cent anhydrous soap basis).

#### ETHICON SUTURE LABORATORIES, INC.

Surgical Soap Gamophen: 56.7 Gm. and 127.5 Gm. cakes. A soap containing 2 per cent hexachlorophene.

U. S. trademark 532,820.

#### J. I. HOLCOMB MANUFACTURING COMPANY

Liquid Soap Hexachlorophene: 3.78, 18.9, 56.7, 113.4 and 208.1 liter containers. A soap containing 0.5 per cent hexachlorophene (2 per cent anhydrous soap basis).

#### HUNTINGTON LABORATORIES, INC.

Germa-Medica Liquid Surgical Soap Hexachlorophene: 3.78 and 18.9 liter cans; 56.7, 75.6, 113.5, 132.4, 208.1 and 245.9 liter drums. A liquid soap containing 1 per cent hexachlorophene (2.5 per cent anhydrous soap basis).

U. S. trademark 213,093.

#### RETORT PHARMACEUTICAL COMPANY, INC.

Surgical Soap Hex-O-San: 3.78 liter and 18.9 liter cans and 56.7 liter, 113.5 liter and 208.1 liter drums. A soap containing 0.72 per cent hexachlorophene (2 per cent anhydrous soap basis).

#### VESTAL, INC.

Septisol with Hexachlorophene 0.75%: 3.78 liter pails and 113.5 and 208.1 liter drums. A soap containing 0.75 per cent hexachlorophene (2 per cent anhydrous soap basis).

U. S. trademark 245,239.

#### WINTHROP-STEARNs, INC.

pHisoHex: 88.7 cc., 473 cc. and 3.78 liter bottles and 148 cc. squeeze bottles. A detergent lotion containing 3 per cent of hexachlorophene (18.4 per cent anhydrous detergent basis).

U. S. patent 2,303,932. U. S. trademark 408,558.

## DYES

Dyes are used in medicine as antiseptics, as chemotherapeutic agents and for special effects upon tissue cells. The local antiseptic action of dyes results from their bacteriostatic and bactericidal powers. These are often specific.

The dyes used in medicine are nearly all organic, synthetic products. They may be roughly divided into six classes: (1) the azo dyes; (2) the acridine dyes, such as acriflavine hydrochloride, acriflavine base and proflavine; (3) the fluorescein dyes, either as



fluorescein or combined with the metal mercury, such as mercurochrome soluble and flumerin; (4) the phenolphthalein dyes such as phenolphthalein and phenolsulfonphthalein-U.S.P. and their chlorine, bromine and iodine substitution products; (5) the triphenylmethane or rosaniline series, a large list of widely used substances, such as gentian violet, crystal violet, methyl violet and fuchsin; (6) miscellaneous dyes, such as methylene blue (methylthionine chloride-U.S.P.). Much confusion exists because of the varying composition of similar dyes produced by different manufacturers of commercial dyestuffs. Usually the commercial dye contains a diluent, such as dextrin or salts, and is judged by tinctorial power. In order to obtain comparable results in the clinic, the dyes should be of constant composition, preferably without diluent.

### Triphenylmethane (Rosaniline) Derivatives

The triphenylmethane (rosaniline) dyes used medicinally are typified by such substances as fuchsin, methylrosaniline chloride (gentian violet) and brilliant green.

Gentian violet has a selective action on gram-positive organisms; in fact, the action of the dye is so selective that often a "strain within a species" is not affected. The selective power of acid fuchsin (the acid sodium salt of fuchsin disulfonic and trisulfonic acids) is in some respects opposite to that of gentian violet, a stained culture of *Ser. marcescens* (*prodigiosus*) being killed by the acid fuchsin, while the gram-positive *B. anthracis* is unaffected, at a temperature of about 50°. Acid fuchsin is incompatible with gentian violet. None of the rosaniline dyes is a strong bactericide.

Rosaniline dyes are employed for the treatment of superficial fungous infections of the skin. Fuchsin, the dye component of carbol-fuchsin paint, is widely employed for this purpose, as are also gentian violet and the acridine dye, acriflavine. The principal disadvantage of these dyes is that they stain clothing.

**CARBOL-FUCHSIN PAINT.**—*Carfusin* (RORER).—A solution containing 1 per cent boric acid, 4.5 per cent phenol, 10 per cent resorcinol, 0.3 per cent fuchsin, 5 per cent acetone and 10 per cent alcohol in water, q. s.

The boric acid, phenol, resorcinol, fuchsin and acetone used in the preparation of this product meet the requirements of the *U. S. Pharmacopeia* or the *National Formulary*.

**Actions and Uses.**—Carbol-fuchsin paint is a stabilized preparation of the original fuchsin formula known as Castellani's paint; it is widely employed for topical application to superficial fungous infections of the skin. Its use should be restricted to subacute or chronic dermatophytoses. It is of value for epidermophytosis interdigitalis pedum ("athlete's foot"), other intertriginous lesions of fungous origin, *Tinea trichophytina* (ringworm) and *Tinea imbricata*.

Carbol-fuchsin paint has the advantage over the original and subsequent preparations in that it is stable, but it must be protected against evaporation. It shares with other triphenylmethane



dyes the disadvantage that it stains clothing. It should never be applied to large areas of the body or to patients who have sensitive skin. A test application of a 1:3 dilution should be made to a single small lesion before treatment is begun with the full strength paint. The ingredients are poisonous.

**Dosage.**—Full strength carbol-fuchsin paint is applied directly to the surface of skin lesions. Topical application once or twice daily is indicated in subacute phases, three times daily in chronic or particularly stubborn lesions. Interim use of a foot powder and twice daily change of hosiery is recommended in the treatment of epidermophytosis pedis. In cases associated with excessive drying of the skin, application of the paint may be continued in conjunction with applications of either boric acid ointment containing 2 to 5 per cent of ammoniated mercury or an ointment of petrolatum containing 1 per cent each of sulfur and salicylic acid and 25 per cent each of zinc oxide and talc.

WILLIAM H. RORER, INC.

**Carfusin:** 30 cc. and 120 cc. bottles. A solution containing 1 per cent boric acid, 4.5 per cent phenol, 10 per cent resorcinol, 0.3 per cent fuchsin, 5 per cent acetone and 10 per cent alcohol in water, q. s.

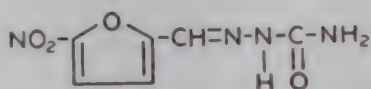
U. S. trademark 509,952.

THE VELTEX COMPANY

**Carbol-Fuchsin Paint:** 30 cc., 60 cc., 120 cc. and 480 cc. bottles. A solution of 1 per cent boric acid, 4.5 per cent phenol, 10 per cent resorcinol, 0.3 per cent fuchsin, 5 per cent acetone, and 10 per cent alcohol in water, q. s.

## NITROFURAN DERIVATIVES

**NITROFURAZONE.**—Furacin (EATON LABS.).—5-Nitro-2-furaldehyde semicarbazone.—The structural formula of nitrofurazone may be represented as follows:



**Physical Properties.**—Nitrofurazone is an odorless, lemon-yellow, crystalline powder, which turns brownish black on heating and decomposes between 236 and 240°. It is nearly tasteless but develops a bitter aftertaste. One part of nitrofurazone is soluble in 590 parts of alcohol, 350 parts of propylene glycol and 4200 parts of water. It is slightly soluble in polyethylene glycol mixtures and is practically insoluble in ether. The crystals darken on prolonged exposure to light.

**Actions and Uses.**—Nitrofurazone is a substituted furan compound possessing bacteriostatic and bactericidal properties; it is inhibitory in broth concentrations of 1:100,000 to 1:200,000 and

bactericidal at 1:50,000 to 1:75,000. It is effective *in vitro* and *in vivo* against a variety of gram-negative and gram-positive bacteria; it has least bacteriostatic activity against *Pseudomonas aeruginosa* and little bactericidal effect on *Diplococcus pneumoniae*.

Experimental evidence indicates that the activity of the nitrofurans against bacteria is due to their interference with essential enzyme systems of the bacterial cells. Induced resistance to sulfathiazole, penicillin or streptomycin does not entail resistance to nitrofurazone.

Nitrofurazone is useful for topical application in the prophylaxis and treatment of superficial mixed infections common to contaminated wounds, burns, ulcerations and pyodermas, especially impetigo and ecthyma. It is also useful topically as an adjunct in the management of acute or chronic purulent otitis of bacterial origin arising from either the external or the middle ear, except in severe otitis media associated with cholesteatoma. It may be useful as an adjunct to surgery in the preparation of areas for skin grafting and in the treatment of osteomyelitis. Daily application for periods of 10 days or longer may produce a local reaction in some cases. Intolerance to local use of nitrofurazone has been observed and may be an indication for withdrawing the drug. Continuous applications for 5 days may produce sensitization and generalized allergic skin reaction. Photosensitization from sunlight has not been encountered.

Systemic toxicity due to absorption of the compound is unlikely.

**Dosage.**—Nitrofurazone is used topically in an ointment-like base or solution containing a concentration of 1:500 (0.2 per cent). It is applied locally either directly or to dressings which are then used to cover the infected area. The base is water soluble, softens at body temperature and may thus require special coverings to maintain effective contact with certain areas. Contact of the ointment with the infecting micro-organisms is essential for their destruction. Dressings may be reinforced with cellophane or similar material, and petrolatum gauze may be used for a barrier to limit absorption into the dressing. On exposure to light, the bright yellow nitrofurazone turns dark brown. This is not associated with any ill effects and may be avoided by covering it with light dressings.

For topical application in the control of purulent otitis, 0.5 cc. of a 0.2 per cent solution is instilled into the external meatus three or four times daily. The application should be preceded with cleansing of the meatus by irrigation and drying. A cotton plug may be inserted after each application to retain the solution, or it may be applied to a gauze wick which is then inserted.

EATON LABORATORIES, INC.

**Ear Solution Furacin 0.2%:** 30 cc. dropper bottles. An anhydrous solution in polyethylene glycol 300.

**Soluble Dressing Furacin 0.2%:** 56.7 Gm. tubes; 113 Gm., 454 Gm. and 2.26 Kg. jars. An ointment containing 2 mg. of nitrofurazone, 0.45 Gm. of polyethylene glycol 1540, 0.05 Gm. of poly-



ethylene glycol 4000, and 0.5 Gm. of polyethylene glycol 300 in each gram.

**Solution Furacin 0.2%:** 118 cc. and 473 cc. bottles. A solution containing 2 mg. of nitrofurazone, 3 mg. of polyethylene glycol of monoisooctyl phenyl ether in a mixture of 0.32 Gm. of polyethylene glycol 300, 0.32 Gm. of polyethylene glycol 1540 and water in each cubic centimeter.

U. S. patents 2,319,481 and 2,416,234. U. S. trademark 403,279.

## HALOGEN COMPOUNDS

### Chlorine Derivatives

Chlorine is the most widely used and one of the most reliable of all chemical disinfectants. Labarraque introduced chlorinated lime as a disinfectant in the French catgut industry in 1829; subsequently, chlorine has been utilized primarily in sanitation engineering and in surgery and obstetrics.

The disinfecting action of chlorine compounds depends on the free chlorine liberated or on the vigorous oxidizing action resulting from their decomposition. Chlorine is used for disinfection of drinking water and swimming pools.

The efficiency of chlorine is greatly reduced by the presence of organic matter, due to its affinity for the protein molecule. It replaces the hydrogen in the alpha-amino groups of the protein molecule to form unstable chloramino acids. For this reason, frequent application of fresh chlorine preparations to wounds is necessary.

Hypochlorite solutions, prepared by combining liquid or gaseous chlorine with a solution of caustic soda, are used principally as bleaches and as convenient sources of chlorine for sanitation. No hypochlorite solution is both stable and rapidly germicidal. Mixtures of sodium hypochlorite and calcium hypochlorite have the advantages of stability and moderate alkalinity and are therefore less caustic. Germicidal efficiency of these solutions requires a maximum of available chlorine in the form of hypochlorous acid. Hypochlorite preparations such as Dakin's solution, in concentrations which are germicidally effective, tend to devitalize tissues and digest blood clots. They have been superseded by less toxic medicaments.

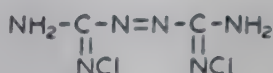
From a group of complex organic compounds, Dakin and Cohen selected one containing a chloramide group as a substitute for the hypochlorites. This and similar derivatives are called chloramines. They combine less readily with organic matter than do the hypochlorites, and exert antibacterial action more slowly. Chloramines are more stable and less irritating to tissue than are hypochlorite solutions of similar strength.

Chlorine is relatively unselective toward micro-organisms. Pathogens of the colon-typhoid group and many of the pathogenic spores are sensitive to its action; *Mycobacterium tuberculosis* resists destruction by chlorine. Filterable viruses are inactivated by chlorine, but it is doubtful that the concentration ordinarily employed in drinking water is sufficient to insure their destruction.



In general, increase in temperature and decrease in acidity increases germicidal activity of chlorine and chlorine compounds.

**CHLOROAZODIN-U.S.P.—Azochloramid** (WALLACE & TIERNAN).— $\alpha,\alpha'$ -Azo-bis(chloroformamidine).—"Chloroazodin contains not less than 97 per cent and not more than 102 per cent of  $C_2H_4Cl_2N_6$ ." *U.S.P.* The structural formula of chloroazodin may be represented as follows:



**Physical Properties.**—Chloroazodin occurs as bright, yellow needles or flakes. It has a faint odor suggestive of chlorine and a slightly burning taste. Solutions of chloroazodin in glycerin and in alcohol decompose rapidly on warming, and all solutions of chloroazodin decompose on exposure to light. Chloroazodin decomposes explosively at about  $155^\circ$ . Its decomposition is accelerated by contact with metals. It is very slightly soluble in water, sparingly soluble in alcohol, slightly soluble in glycerin and in glyceryl triacetate and very slightly soluble in chloroform.

**Actions and Uses.**—The actions and uses of chloroazodin are similar to those of a dilute solution of sodium hypochlorite and the other chloramines. However, it does not hydrolyze appreciably in aqueous solutions and it has a low rate of reaction with mild reducing agents and other organic matter. Consequently, its concentration does not decrease rapidly and it exerts a more prolonged and stronger bactericidal action in the presence of tissue fluids and exudate than the other chloramines. Solutions of chloroazodin are used on dressings for wounds and on packings for infected cavities. Aqueous solutions are suitable for lavage of wounds, and for irrigations of and instillations into cavities. Short exposure of epithelial tissue to aqueous solutions is harmless. Chloroazodin possesses low toxicity and is a nonselective bactericide.

**Dosage.**—Chloroazodin is usually employed in wounds in a dilution of 1:3,300 in an approximately isotonic solution buffered at pH 7.4. Greater dilutions, up to 1:13,200, are proposed for use on mucous membranes. On dressings and packings the stable solution of 1:500 in glyceryl triacetate (triacetin) is used. Gauze impregnated with the triacetin solution of chloroazodin does not dry out or stick to the wound. A solution prepared by mixing one volume of a strong solution of chloroazodin in triacetin (1:125) with 19 volumes of a vegetable oil contains one part of chloroazodin in 2,000 parts (by weight) of the solution and is sufficiently bland to be applicable to mucous membranes of the vagina, colon and rectum.

WALLACE & TIERNAN, INC.

**Powder Saline Mixture of Azochloramid:** Bottles of the powder containing 36 Gm. for preparing 1 gallon of aqueous solution of chloroazodin (1:3,300) contain 3.2 per cent chloroazodin, 89.6

per cent sodium chloride, 1 per cent monopotassium phosphate and 6.3 per cent anhydrous sodium phosphate by weight.

**Solution Azochloramid in Triacetin (1:500):** 59 cc., 236 cc., 946 cc. and 3.78 liter containers. A solution containing 1 Gm. chloroazodin in 500 Gm. of triacetin. Triacetin is a mixture of glyceryl acetates containing approximately 95 per cent of glyceryl triacetate.

**Strong Solution Azochloramid in Triacetin (1:125):** 50 cc. bottles. A solution containing 1 Gm. chloroazodin in 125 Gm. triacetin for use in the preparation of chloroazodin in vegetable oil (1:2,000).

**Tablets Saline Mixture of Azochloramid:** Each tablet contains 18 mg. of chloroazodin in buffered saline mixture for the preparation of 60 cc. of aqueous solution (1:3,300).

U. S. trademark 322,242.

## Iodine and Derivatives

Certain iodine compounds are used for their local irritant and antiseptic effects, which are due probably to the action of free iodine contained in the preparations or liberated from them; or they may be administered for their systemic actions and for roentgen-ray diagnosis.

**DIGLYCOCOLL HYDROIODIDE-IODINE.—Bursoline (BURNHAM SOLUBLE IODINE).**—Two moles of diglycocoll hydroiodide combined with two atomic weights of iodine. It contains 30.5 to 32.0 per cent of active iodine. The formula of diglycocoll hydroiodide-iodine may be represented as follows:



**Physical Properties.**—Diglycocoll hydroiodide-iodine is a dark, almost black, lumpy powder with a strong odor of iodine. It is freely soluble in water and practically insoluble in chloroform. Although it is only very slightly soluble in alcohol, the iodine component is soluble. The pH of a 0.1 per cent solution of diglycocoll hydroiodide-iodine is about 3.0.

**Actions and Uses.**—Diglycocoll hydroiodide-iodine is a preparation used in the form of tablets to provide a convenient source of readily soluble iodine for the disinfection of drinking waters. Amounts of the preparation sufficient for disinfection of water are well below the toxic level. It produces a slight iodine taste and color which are reasonably tolerable. Its advantage over simple iodine solutions for the disinfection of water is its dry, stable form which permits it to be carried more conveniently. The effect of diglycocoll hydroiodide-iodine on such a virus as epidemic hepatitis virus, which is infrequently found in drinking water, is not known.

**Dosage.**—Diglycocoll hydroiodide-iodine is supplied only in the



form of tablets, each of which contains 16.4 mg. of total iodine and provides an average titratable iodine concentration of 7.4 p.p.m. when added to one liter of water. One tablet per liter reduces *Escherichia coli*, *Salmonella typhosa*, *Shigella dysenteriae* and *Salmonella schottmulleri* from concentrations of about  $50 \times 10^6$  to  $100 \times 10^6$  per 100 cc., to an average of 1 to 5 organisms per 100 cc. (most probable number) at 25° in normal, slightly polluted, alkaline, turbid and cold (7°) waters. One tablet per liter is cysticidal at 23° within 5 minutes in normal waters; in moderately polluted, alkaline and turbid waters, within 10 minutes; and in cold water (5°), within 20 minutes. To disinfect waters rich in leaf extract, two tablets should be used per liter of water. The highest iodine demands are not associated with water containing organic nitrogen, such as sewage, but with waters in which there is much decomposed vegetable matter. The iodine demand of waters is less in acid than in basic solutions and it appears to be equal to or less than the chlorine demand.

The tablets should be protected against moisture from the air, but are otherwise stable and maintain effectiveness for 3 months even under conditions involving a temperature of 140° F.

Water on the lips of containers in which disinfection is carried out does not come in contact with the iodine or form a part of the measured portion being disinfected; therefore, these should not be used as drinking receptacles until the treated portion has been allowed to run across such areas to eliminate all untreated water.

#### BURNHAM SOLUBLE IODINE COMPANY

**Tablets Bursoline:** Each tablet contains 8.2 mg. of iodine, 18 mg. of diglycine hydroiodide and 88.8 mg. of sodium acid pyrophosphate.

U. S. trademark 422,297.

## METAL COMPOUNDS

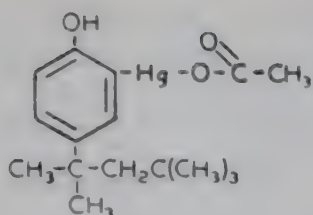
### Mercury

Compounds of mercury are used for the preparation of antiseptic and disinfectant solutions. They have limited germicidal action and cannot be relied upon to kill bacterial spores. Because of their bacteriostatic action solutions of mercury compounds with dyes or other organic radicals are used for antiseptics of the skin. These organic compounds of mercury are less toxic and less irritating than the older chlorides, iodides and cyanides of mercury. Their ability to penetrate deeply into living tissue has not been established. Their antibacterial activity is greatly diminished in the presence of serum and other proteins.

### Organic

**ACETOMEROCTOL.**—Merbak (SCHIEFFELIN).—2-Acetoxymercuri-4-(1,1,3,3-tetramethylbutyl)phenol.—The structural formula of acetomeroctol may be represented as follows:





**Physical Properties.**—Acetomerocetol is a white solid which melts between 155 and 157°. It is freely soluble in alcohol, soluble in ether and chloroform, sparingly soluble in benzene and practically insoluble in water.

**Actions and Uses.**—Acetomerocetol, an organomercurial, is employed as a topical antiseptic for the prevention and control of superficial infection. It is subject to the same limitations of usefulness as other organic mercurial antiseptics. The alcohol-acetone solution accounts for a significant part of the antibacterial action of the preparation. These components may produce irritation when used on mucous membranes or extensive superficial wounds.

**Dosage.**—Acetomerocetol is applied locally in 1:1,000 solution containing 50 per cent alcohol and 10 per cent acetone.

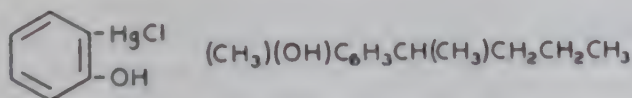
#### SCHIEFFELIN & COMPANY

**Tincture Merbak 1:1,000 (Colored):** 30 cc., 118 cc., 473 cc. and 3.78 liter bottles. A solution of 50 per cent alcohol and 10 per cent acetone containing 1 mg. acetomerocetol in each cubic centimeter.

**Tincture Merbak 1:1,000 (Stainless):** 118 cc., 473 cc. and 3.78 liter bottles. A solution of 50 per cent alcohol and 10 per cent acetone containing 1 mg. acetomerocetol in each cubic centimeter.

U. S. patent 2,415,754.

**MERCOCRESOLS.**—**Mercresin (UPJOHN).**—A mixture consisting of equal parts by weight of *sec.*-amyltr cresol and *o*-hydroxyphenylmercuric chloride. Mercocresols is used in the form of a tincture containing 0.1 per cent secondary amyltr cresol and 0.1 per cent *o*-hydroxyphenylmercuric chloride dissolved in a solution containing 10 per cent acetone, 50 per cent alcohol, and water. The structural formula of mercocresols may be represented as follows:



**Actions and Uses.**—Mercocresols, the combination of cresol derivatives and an organic mercury compound, possesses germicidal, fungicidal and bacteriostatic properties peculiar to its two active parts. The actions of the two constituents supplement each other so that the mixture is approximately twice as germicidal for *Staphylococcus aureus* as the component cresol derivatives alone, and seven to ten times as germicidal as the mercury compound alone. The estimated total effect is not of that order for all patho-

genic bacteria and should be understood to represent a summation of activity rather than synergistic action of the two components. Mercocresols, used as a germicide, is subject to some of the shortcomings of ordinary tricesols and organic mercurial antiseptics, particularly in its inability to destroy bacterial spores.

The tincture of mercocresols described above is applied externally as an antiseptic for minor superficial wounds or infections and as a prophylactic disinfectant for surgical preparation of the intact skin. In the dilutions below it is useful for topical application to mucous membranes and for irrigation of certain body cavities and deep infected wounds.

The toxicity of mercocresols is principally that of the organic mercurial component.

**Dosage.**—Mercocresols is applied topically in the undiluted tincture (containing secondary amylicresol 1:1,000 and *o*-hydroxyphenylmercuric chloride 1:1,000) to all superficial wounds and for surgical preparation of the intact skin. It may be similarly applied to the ear, nose and throat, but dilutions of 1:5 to 1:20 should be used for irrigation or wet packs applied to these surfaces. In general, 1:2 to 1:20 dilutions are used for topical application, irrigation or tamponage of inflamed mucous membranes depending on the site and the method employed. For irrigation of deep infected wounds or abscesses, dilutions of 1:5 to 1:10 are recommended; for irrigation, instillation or lavage of the bladder and urethra dilutions of 1:10 to 1:20 should be used. Dilutions of 1:10 to 1:20 are also employed for instillation in the eye.

Mercocresols is compatible with both acids and alkalies and does not precipitate with the chlorides of the body fluids.

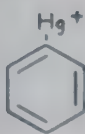
#### THE UPJOHN COMPANY

**Tincture Mercresin:** 60 cc. (Pistol Grip), 118 cc., 473 cc. and 3.785 liter bottles. A tinted solution of 0.2 per cent mercocresols, in a mixture of 10 per cent acetone, 50 per cent alcohol and water.

**Tincture Mercresin (Stainless):** 118 cc., 473 cc. and 3.785 liter bottles. An untinted solution of 0.2 per cent mercocresols in a mixture of 10 per cent acetone, 50 per cent alcohol and water.

#### PHENYLMERCURIC COMPOUNDS

Phenylmercuric chloride and basic phenylmercuric nitrate were the first organic mercurial compounds of their type found to possess effective bacteriostatic and bactericidal activity against certain pathogenic micro-organisms. Evidence that other phenylmercuric salts are similarly effective suggests that the activity of such compounds is primarily attributable to the phenylmercuric ion, the structural formula of which may be represented as follows:





In general, phenylmercuric salts are highly dissociable in solutions, providing phenylmercuric ions, effective concentrations of which depend on the widely varying solubility of the salts employed. In acid, neutral or slightly alkaline solutions, chlorides, bromides, iodides and soaps react with phenylmercuric ion to precipitate a phenylmercuric salt. Phenylmercuric chloride is soluble only to the extent of 1 part in 20,000 of water, the bromide is still less soluble and the iodide is insoluble. For this reason the chloride has been supplanted by the more soluble basic phenylmercuric nitrate and other salts.

The phenylmercuric ion ( $\text{C}_6\text{H}_5\text{Hg}^+$ ) is more stable in acid than in alkaline solutions of its salts. Aqueous solutions containing phenylmercuric ions, buffered with inorganic or organic acids, are fairly stable. In the presence of organic solvents the stability is less but still satisfactory. Because buffered solutions of phenylmercuric salts are more stable and also less irritating to tissue than unbuffered solutions, they are preferred for pharmaceutical purposes. In general, the buffered solutions are stainless, colorless, odorless, without action on rubber and noncorrosive to the common metals other than aluminum, except as these properties may be influenced by the particular acid employed. Solutions of phenylmercuric salts may develop increasing amounts of mercuric and mercurous ions or free mercury as the result of gradual decomposition of phenylmercuric ions.

Phenylmercuric compounds are of comparatively high germicidal and inhibitory value against a variety of pathogenic bacteria and of relatively low toxicity to human tissue. Like other types of organic mercurial antiseptics, however, they cannot be depended on to kill bacterial spores. The presence of buffered solutions of phenylmercuric salts does not interfere with the precipitin reaction of human serum, the action of complement, the digestive action of pepsin and trypsin or the antigenic power of vaccine. Despite their low toxicity, phenylmercuric compounds may produce irritation, "burns" or poisoning in occasional individuals with undue sensitivity. In rabbits the minimum lethal intravenous dose of a 0.067 per cent (1:1,500) aqueous solution of basic phenylmercuric nitrate (buffered with 0.1 per cent boric acid) is 7 cc. per kilogram of body weight. The minimum lethal oral dose for these animals is approximately three times the intravenous dose. The toxicity of solutions of this and other phenylmercuric salts varies according to the concentration of phenylmercuric ions, the presence of organic solvents, the acid which is added as a buffer to render them stable and the degree of decomposition. The appearance of metallic mercury as a precipitate in solutions of phenylmercuric salts indicates extensive decomposition.

**PHENYLMERCURIC NITRATE-N.F.—Merphenyl Nitrate (Basic)** (HAMILTON). — Basic Phenylmercuric Nitrate. — "Phenylmercuric Nitrate is a mixture of phenylmercuric nitrate and phenylmercuric hydroxide containing not less than 62.75 per cent and not more than 63.50 per cent of Hg." *N.F.*

*Physical Properties.*—Phenylmercuric nitrate occurs as a white,



crystalline powder. It is affected by light, and its saturated solution is acid to litmus paper. It is very slightly soluble in water and slightly soluble in alcohol and in glycerin. It is more soluble in the presence of either nitric acid or alkali hydroxides.

**Actions and Uses.**—Solution or ointment of phenylmercuric nitrate is used externally as an antiseptic for the prophylactic and therapeutic disinfection of the skin, superficial abrasions, lacerations, wounds and infections.

**Dosage.**—For prophylactic disinfection of the intact skin and minor lesions the aqueous buffered solution 1:1,500 may be applied full strength; for application to mucous membranes or for the application of wet dressings or continuous irrigation to wounds an aqueous solution 1:15,000 to 1:24,000 should be used (prepared by diluting 1 part of the buffered solution 1:1,500 with 10 to 15 parts of water). When used as a wet dressing, the 1:24,000 dilution should be prevented from becoming too concentrated, as the result of unavoidable evaporation, by the addition of 0.5 per cent of sodium chloride. To each 500 cc. of diluted solution, 2.5 Gm. of noniodized table salt may be added. This does not produce excessive precipitation. The full strength (1:1,500) solution should never be used to wet bandages or dressings. The 1:1,500 oxycholesterin base ointment may also be employed for the prophylactic disinfection of minor injuries or may be applied twice daily for the treatment of superficial infections.

HAMILTON LABORATORIES, INC.

**Ointment Merphenyl Nitrate (Basic) 1:1,500:** 28.3 Gm. tubes. A water-in-oil emulsion ( $\frac{2}{3}$  aqueous,  $\frac{1}{3}$  oil phase) of an oxycholesterin base containing 0.067 per cent basic phenylmercuric nitrate with 0.1 per cent boric acid.

**Solution Merphenyl Nitrate (Basic) 1:1,500:** 473 cc. and 3.78 liter bottles. An aqueous solution containing 0.067 per cent basic phenylmercuric nitrate with 0.1 per cent boric acid.

U. S. trademark 318,039.

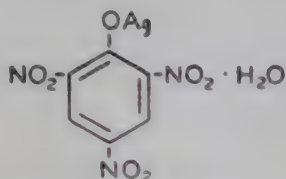
## Silver

Silver compounds are used in medicine to secure caustic, astringent and antiseptic effects. These results are produced by the free silver ions. When caustic effects are desired, silver nitrate is preferred, because the colloidal compounds of silver are not caustic. As an astringent, also, silver nitrate is the compound of choice, but it must be used in weaker solutions; silver picrate acts similarly. The antiseptic action of silver nitrate is complicated by irritation, pain, astringency and corrosion. These may be desirable for the destruction of tissue or the stimulation of indolent wounds; but when they are not necessary, these actions may be avoided by the use of colloidal silver preparations.

**Caution.**—*The long continued use of any silver preparation may produce irremediable discoloration of the skin or mucous membrane (argyria).*

### Silver Salts

**SILVER PICRATE.**—Picragol (WYETH).—Silver trinitrophenolate monohydrate.—The structural formula of silver picrate may be represented as follows:



**Physical Properties.**—Silver picrate forms yellow crystals, which slowly discolor in sunlight. It is sparingly soluble in alcohol and water, slightly soluble in acetone and glycerin and very slightly soluble in chloroform and ether.

**Actions and Uses.**—Silver picrate is used in the treatment of vaginitis due to *Trichomonas vaginalis* and *Monilia albicans* in the form of a compound powder for insufflation and suppositories for insertion. Protracted use of this compound over a long period may give rise to argyria because of its silver content and nephritis because of its picric acid content. It is therefore necessary to watch the skin for signs of argyria, and the urine for albumin and casts. In all vaginal insufflation in the pregnant female, the physician should exercise every precaution to prevent positive pressure in the vagina because of danger of breaking the enlarged veins and introducing air into the venous circulation.

**Dosage.**—Concentrations of 1 to 2 per cent are used in the form of compound powder and vaginal suppositories.

The compound powder is administered by means of an insufflator or other surgical "powder blower." The vaginal suppository containing 0.13 Gm. in a boroglyceride gelatin base is intended primarily to be used as an adjunct in the treatment of this condition.

WYETH LABORATORIES, INC.

**Powder Picragol Compound 1%:** 5 Gm. bottles. 1 per cent silver picrate in purified kaolin.

**Vaginal Suppositories Picragol:** 0.13 Gm. silver picrate in a boroglyceride gelatin base.

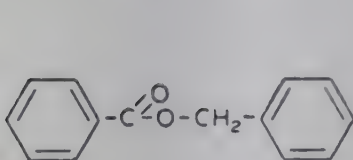
U. S. trademark 421,338.

### PEDICULICIDES

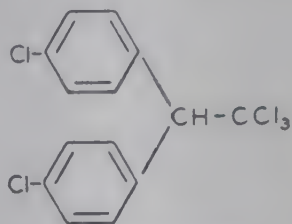
**GAMMA BENZENE HEXACHLORIDE.**—For the monograph, see the section on scabicides.

**BENZYL BENZOATE-CHLOROPHENOTHANE-ETHYL AMINO-BENZOATE.**—Enbin (WILLIAM COOPER).—Available as oil-in-water emulsions, one of which is included in the *U. S. Pharmacopeia* as benzyl benzoate chlorophenothane lotion. They contain benzyl

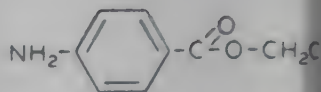
benzoate-U.S.P., chlorophenothane-U.S.P. (D.D.T.) and ethyl aminobenzoate-U.S.P. The structural formulas of these compounds may be represented as follows:



Benzyl benzoate



Chlorophenothane



Ethyl aminobenzoate

**Physical Properties.**—This mixture, as a lotion, is a milky liquid when it is shaken to resuspend the solids.

**Actions and Uses.**—The mixture benzyl benzoate-chlorophenothane-ethyl aminobenzoate is used for the treatment of pediculosis and scabies. The primary ingredient, a 1 per cent concentration of chlorophenothane, destroys lice; the 2 per cent concentration of benzocaine is an effective ovicide. Benzyl benzoate added in a concentration of 10 per cent or more is effective as a scabicide and to a lesser extent as a pediculicide. Although the mixture is effective against both of these types of skin parasites, it should not be carelessly employed for undiagnosed itching. When scabies alone is the cause, the use of benzyl benzoate is more rational than the application of the mixture. There have been no reports of systemic effects or skin irritation following occasional applications of the mixture. Temporary smarting of tender areas of skin occurs. Because sensitization may follow, repeated applications should be avoided. Chlorophenothane has infrequently produced allergic eczematous dermatitis on repeated contact with the skin.

**Dosage.**—For pediculosis, either an emulsion or ointment of the mixture should be evenly applied by rubbing in an amount (usually about 60 cc. or Gm.) just sufficient to dampen all hair of the region involved and to anoint the underlying scalp or skin. This should remain in contact with the affected areas for 24 to 48 hours and then be removed by washing hair or bathing skin with soap and warm water. It may be necessary to repeat treatment in pediculosis capitis if the hair is washed within a week after treatment. All clothing should be thoroughly laundered or dry cleaned and uncontaminated apparel used after treatment.

For scabies, a preliminary warm, soapy bath should be taken and all contaminated clothing laundered or dry cleaned to prevent reinfestation. All soap should be rinsed from the skin. Either a liquid emulsion or an ointment of the mixture is applied by rubbing over the entire body surface below the neck. All folds of the skin and areas beneath the nails must be treated. The application should be allowed to remain on the skin for at least 24 hours before bathing. The treatment should also be reapplied to the hands after each washing during the treatment period.

One application is usually sufficient to control either pediculosis or scabies, but the application may be repeated after a week if

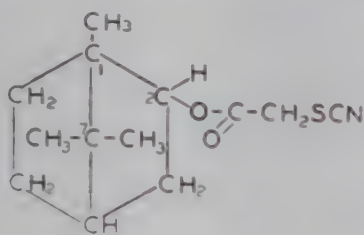


necessary. All contact with the eyes or other mucous membranes should be avoided. To minimize possible irritation in infants, the emulsion of the mixture should be diluted to half strength by adding an equal amount of distilled water.

WILLIAM COOPER & NEPHEWS, INC.

**Emulsion Enbin:** 90 cc. bottles. An emulsion containing 0.113 Gm. of benzyl benzoate, 10 mg. of chlorophenothane and 20 mg. of ethyl aminobenzoate in each cubic centimeter. Stabilized with polyox-alkylene derivative of sorbitan monooleate.

**ISOBORNYL THIOCYANOACETATE-TECHNICAL.**—Bornate (WYETH).—The technical grade of isobornyl thiocyanacetate contains 82 per cent or more of isobornyl thiocyanacetate with other terpenes. The structural formula of isobornyl thiocyanacetate may be represented as follows:



**Physical Properties.**—Isobornyl thiocyanacetate-technical is a yellow, oily liquid with a terpenelike odor. It is very soluble in alcohol, benzene, chloroform and ether and practically insoluble in water. Its specific gravity is about 1.1465 and its acid number is about 1.19.

**Actions and Uses.**—Isobornyl thiocyanacetate is one of the thiocyanates effective as a pediculicide. A mixture of the technical grade of this compound with dioctyl sodium sulfosuccinate in the form of an oil emulsion is useful for external application to eradicate both the adult and ova forms of *Phthirus pubis*, *Pediculus humanus capitis* and *Pediculus humanus corporis*. The compound may act as a mild primary irritant to the skin of some individuals, but there is no evidence that it acts as a sensitizing agent. *It should not be applied near the eyes or to mucous membranes.*

**Dosage.**—An oil emulsion containing 5 per cent isobornyl thiocyanacetate (technical) and 0.6 per cent dioctyl sodium sulfosuccinate is applied externally in amounts of 30 to 60 cc., depending on the site (amount of hair), worked into a lather and allowed to remain for 10 minutes. In treatment of the scalp, the hair is then combed with a fine-tooth comb and washed with a bland soap and water. On the body, the emulsion is worked well into the hair and then washed off with bland soap and water. Care must be taken that the emulsion does not remain in contact with the skin too long. More than two such applications should be avoided.

WYETH LABORATORIES, INC.

**Lotion Bornate:** 60 cc. and 3.785 liter bottles. An emulsion containing 5 per cent isobornyl thiocynoacetate, 0.6 per cent dioctyl sodium sulfosuccinate, in 5 per cent mineral oil, 0.6 per cent gelatin and water.

## PEROXIDES

The peroxides belong to a class of oxidizing agents (others: chlorine, ozone, perborates, permanganates) which are deleterious to bacteria by virtue of the nascent oxygen they liberate. Nascent oxygen combines rapidly with all organic matter and once combined is inert; these properties reflect the strength and weakness of these agents as germicides. All of these agents are rapidly inactivated by catalase, a ferment found in most cells. Molecular oxygen is harmful only to obligate anaerobes which produce hydrogen peroxide but do not produce catalase with which to destroy it.

Hydrogen peroxide,  $H_2O_2$ , decomposes to water and one atom of nascent oxygen. Solutions of hydrogen peroxide have high surface tensions and therefore do not penetrate well. Because of their rapid inactivation by protein, they must be used over a long period of time. The strong (30 per cent) solution is extremely caustic; the 3 per cent commercial solutions have little germicidal value.

The liberated oxygen from hydrogen peroxide decomposition sometimes causes effervescence. For this reason it should not be injected into closed body cavities or into abscesses from which the gas cannot escape.

Hydrogen peroxide is valuable for the removal of dead organic matter from areas from which mechanical removal is difficult. Its action on bacteria increases with increased temperature and in the presence of certain salts which catalyze the release of nascent oxygen from the stabilized solutions. It is effective against some gram-negative and some gram-positive bacteria. It inhibits the growth of anaerobic organisms, although this action is transitory. In concentrations which are nontoxic to tissues it is incapable of destroying spores.

In metallic peroxides the hydrogen of hydrogen peroxide has been replaced by metals, which slowly liberate oxygen for 24 to 48 hours. They differ in action in accordance with their solubility and the alkalinity produced by interaction of the peroxide with water. The action of peroxides is also affected by the nature of the metal which goes into solution when the peroxide is decomposed. Thus, the use of sodium peroxide is limited because a strong base is formed when it dissolves in water.

Zinc peroxide is used postoperatively to control infection although it is not effective against all micro-organisms and the consistency of the preparations precludes deep infiltration. Disintegration of zinc peroxide leaves deposits of zinc oxide and hydroxide in the wound and increases exudation. Untoward drying of the medicament may be prevented by properly covering the area with petrolatum or zinc oxide ointment gauze.



**ZINC PEROXIDE, MEDICINAL-U.S.P.**—"Medicinal Zinc Peroxide consists of a mixture of zinc peroxide, zinc carbonate and zinc hydroxide. Each Gm. of Medicinal Zinc Peroxide, previously heated at 135° to 140° for 4 hours, evolves not less than 2.16 cc. of oxygen in 20 hours and not less than 0.24 cc. of oxygen in the following 4 hours." *U.S.P.*

**Physical Properties.**—Medicinal zinc peroxide occurs as a fine, white or faintly yellow, odorless powder. It is almost insoluble in water and organic solvents but dissolves readily in dilute acids.

**Actions and Uses.**—See the general statement on peroxides.

**Dosage.**—Zinc peroxide medicinal (powder) sterilized in small quantities (10 to 50 Gm.) by heating in a dry oven for 4 hours at exactly 140° is made up with sterile distilled water to a smooth, creamy suspension of about the consistency of heavy cream. If the suspension is too thin it runs off. If it is too thick it may not come in contact with all surfaces in the crevices of the wound.

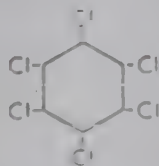
The dose depends entirely on the size of the wound to be treated. Enough of the creamy suspension should be used to provide the surface of the wound with a layer approximately one eighth inch thick. The first layer, applied readily with a syringe, is then covered over with a thin layer of cotton soaked in the suspension and this in turn is covered with a thick layer of cotton wet with water and then sealed with an impermeable covering or coating of some kind. Dressings are usually changed in 24 hours but may be left for several days.

#### MALLINCKRODT CHEMICAL WORKS

Powder Zinc Peroxide Medicinal: 28.3 Gm., 113.4 Gm. and 454 Gm. bottles.

## SCABICIDES

**GAMMA BENZENE HEXACHLORIDE.**—*Gexane* (STRASENBURGH).—*Kwell* (COMMERCIAL SOLVENTS).—Gamma isomer of 1,2,3,4,5,6-hexachlorocyclohexane.—The structural formula of benzene hexachloride may be represented as follows:



**Physical Properties.**— $\gamma$ -Benzene hexachloride is a white, crystalline powder with a slight, musty odor. It melts (U.S.P. method) at about 112° and freezes (cryoscopic method described later in the assay) not lower than 112.19°. One part of  $\gamma$ -benzene hexachloride is soluble at 20° in 6.6 parts of glacial acetic acid, 1.3 parts of acetone, 14.6 parts of alcohol, 2.5 parts of benzene, 3.2 parts of chloroform and 38 parts of ether. It is slightly soluble in ethylene glycol and practically insoluble in water.



**Actions and Uses.**— $\gamma$ -Benzene hexachloride is applied to the skin as a scabicide and pediculicide. Because the drug is highly toxic its application to man must be supervised by a physician. Animal experiments indicate that it may be readily absorbed through the skin. It may however be safely used in concentrations up to 1 per cent if prolonged or repeated application is avoided. A single application is usually adequate to eliminate the active parasites; a second or third application may be required on rare occasions. The nits are not dissolved. It is somewhat irritating to mucous membranes and should not be permitted to come in contact with the eyes. The presence of secondary infection does not interfere with its use, but other appropriate measures may be required to control such complications.

**Dosage.**— $\gamma$ -Benzene hexachloride is applied topically as a lotion or ointment containing up to 1 per cent. Usually not more than 30 cc. of such a preparation is sufficient for a single treatment. It should be applied directly to the involved areas of the skin or hair and to a sufficient surrounding noninvolved area to insure adequate treatment. When the preparation is applied to the scalp, a towel should be worn over the head for one hour after application and, in the case of female patients, it may be advisable to cut the hair before treatment. A small brush may be used to facilitate thorough application to the scalp. All clothing and bed linen should be thoroughly sterilized by boiling to prevent reinfection; wool garments should be dry cleaned. Patients should be instructed not to bathe or wash the hands or hair for at least 24 hours after treatment. A second application may be made after one week if the first is not successful. It is recommended that  $\gamma$ -benzene hexachloride be applied no more than three times as repeated use may irritate the skin.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Gamma Benzene Hexachloride:** Bulk; for manufacturing use.

#### COMMERCIAL SOLVENTS CORPORATION

**Lotion Kwell 1%:** 60 cc. and 473 cc. bottles. A lotion containing 10 mg. of  $\gamma$ -benzene hexachloride in each cubic centimeter.

**Ointment Kwell 1%:** 56.7 Gm. tubes and 454 Gm. jars. An ointment containing 10 mg. of  $\gamma$ -benzene hexachloride in each gram.

U. S. trademark 503,133.

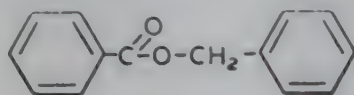
#### R. J. STRASENBURGH COMPANY

**Liquid Gexane 1%:** 59.14 cc., 473 cc. and 3.78 liter bottles. A lotion containing 10 mg. of  $\gamma$ -benzene hexachloride in each cubic centimeter.

**Ointment Gexane 1%:** 21.26 Gm. tubes and 454 Gm. jars. An ointment containing 10 mg. of  $\gamma$ -benzene hexachloride in each gram.

**BENZYL BENZOATE-U.S.P.**—Benylate (BRFON).—Vanzoate (VAN-PELT & BROWN).—"Benzyl benzoate contains not less than 99 per

cent of  $C_{14}H_{12}O_2$ ." *U.S.P.* The structural formula of benzyl benzoate may be represented as follows:



**Physical Properties.**—Benzyl benzoate is a clear, colorless, oily liquid having a slight aromatic odor and a sharp, burning taste. It is insoluble in water and in glycerin. It is miscible with alcohol, with ether and with chloroform. It congeals at a temperature not below  $18^{\circ}$ .

**Actions and Uses.**—Benzyl benzoate applied externally in the form of a 10 to 30 per cent emulsion or lotion has been found to be an effective scabicide. Although it is reported to be effective also as a pediculicide, its use for pediculosis uncomplicated by scabies is not recommended. Application is occasionally followed by a slight, transitory burning sensation. Severe skin irritation may occur occasionally in patients with particularly sensitive skin. Benzyl benzoate should never be allowed to come in contact with the eyes.

**Dosage.**—A 10 to 30 per cent lotion or emulsion of benzyl benzoate is applied with a swab or brush over the entire body surface (*except the face*) while the skin is still damp immediately following scrubbing of the lesions in a 10-minute bath in soap and warm water. Care should be taken to insure application to and around the nails. The first application is allowed to dry and a second application made to the most involved areas. Children ordinarily require 60 to 90 cc. and adults 120 to 180 cc. for a single treatment. Adequate sterilization of bed and body clothing is essential. Twenty-four hours later, clean clothing is put on after a warm soaking bath. A second or third treatment following the same routine should be carried out if necessary to eradicate the parasite. Secondary pyogenic infections do not contraindicate treatment, but should be appropriately treated.

#### THE BLUE LINE CHEMICAL COMPANY

**Lotion Benzyl Benzoate:** 473 cc. and 3.78 liter bottles. An oil-in-water emulsion containing about 28 per cent w/w of benzyl benzoate, 0.5 per cent triethanolamine and 2 per cent oleic acid.

#### GEORGE A. BREON & COMPANY

**Lotion Benylate:** 118 cc. and 473 cc. bottles. An oil-in-water emulsion containing 25 per cent of benzyl benzoate and approximately 2 per cent of triethanolamine stearate. The product is required to be labeled as Modified Benzyl Benzoate Lotion because it differs from the official benzyl benzoate lotion-*U.S.P.* essentially in the emulsifying agent used in its preparation.

#### VANPELT & BROWN, INC.

**Lotion Vanzoate:** 118 cc. and 3.78 liter bottles. A suspension containing 0.28 Gm. of benzyl benzoate in each cubic centimeter. Preserved with 0.009 per cent *n*-butyl *p*-hydroxybenzoate.

U. S. trademark 415,423.



## VELTEX COMPANY

**Lotion Benzyl Benzoate:** 450 cc. and 3.84 liter bottles. An oil-in-water emulsion containing 25 per cent v/v of benzyl benzoate, 0.5 per cent triethanolamine and 2 per cent oleic acid.

**BENZYL BENZOATE-CHLOROPHENOTHANE-ETHYL AMINO-BENZOATE.**—For monograph see the section on pediculicides.

**PYRETHRUM.**—An extract obtained by treating powdered pyrethrum flowers (*Crysanthemum cinerariaefolium*) with a hydrocarbon oil of the kerosene type.

**Physical Properties.**—Pyrethrum ointment is an unctuous, yellowish green mass.

**Actions and Uses.**—Pyrethrum applied as an ointment is effective in the treatment of scabies. The ointment penetrates the burrows and kills both the mites and the eggs and, except in rare instances, it does not produce dermatitis with resultant exfoliation.

**Dosage.**—Pyrethrum is applied as an ointment to the entire body following a thorough cleaning with soap and water. Further applications are made on at least 3 or 4 successive days. In most cases it is necessary to continue the treatment for 5 to 7 days, and in obstinate cases for a longer time. Pyrethrum should not be prescribed for patients who are sensitive to pyrethrum flowers.

## UPSHER SMITH COMPANY

**Ointment Pyrethrum:** 100 Gm. jars. An ointment containing 27 per cent of the active extract (representing 0.75 per cent of pyrethrine I and II) in an ointment base composed of hydrous wool fat, petrolatum and paraffin.

## SURFACE-ACTIVE ANTI-INFECTIVES

Interference with the physicochemical properties of micro-organisms and resultant changes in bacterial metabolism are effected by antiseptics and disinfectants. Certain of these substances have the property of altering surfaces and interfaces; chemical agents which act as local anti-infectives and possess this property are referred to as "detergents." They are subclassified as anionic, cationic and nonionic on the basis of the varying activity encountered in salts that have one ion of much greater molecular weight than the other, on the postulation that un-ionized complexes are formed between chemical agents and micro-organisms.

None of these compounds possesses virucidal, sporicidal or fungicidal properties, nor are they effective against acid-fast bacteria.

Attempts have been made to correlate the ability of these compounds to reduce surface tension with their anti-infective action. That this factor alone is not responsible for their antibacterial action is apparent from the fact that many substances which are good surface-tension depressors are poor anti-infectives. Also, at the concentrations at which the surface-active agents act as anti-infectives, the surface tension does not differ appreciably from that of a good culture medium. Certain types of surface-tension depressors



have been employed in culture media to enhance and accelerate the growth of acid-fast micro-organisms.

*The antibacterial action of all surface-active agents is greatly reduced in the presence of organic matter (i.e., blood serum, pus, etc.) In vitro methods which do not utilize organic matter in the antibacterial evaluation of surface-active agents are of little value and cannot be interpreted as conditions of actual use.*

### Anionic

These agents are the neutral or faintly alkaline sodium (etc.) salts of acids of high molecular weight, exemplified by common soaps, ammonium and calcium mandelates, alkyl sulfates, salts of bile acids and a class of neutral, colored substances known as "acid dyes" (e.g., acid fuchsin).

These agents are effective only on substances at pH values more acid than that of blood; they have been found useless in infected wounds, moderately useful in skin disinfection, and very effective in the disinfection of the urinary tract, provided sufficient acidity is maintained and the substances (i.e. mandelates) are excreted unchanged.

The anionic agents are, in general, most effective against the gram-positive organisms.

Theories concerning their mode of action on the bacterial cell include : (1) possible interaction of their acidic ions with the basic groups (i.e., enzyme systems) of the cell to form feebly ionized compounds and (2) interpretation of increased action in an acid medium to mean that the undissociated acid is more "active" than the ion. The latter theory would lose ground if it were found that increasing the acidic nature of the anions raised their antibacterial action.

Anionic compounds inactivate cationic agents.

**MANDELIC ACID DERIVATIVES.**—See the chapter on systemic anti-infectives.

**SODIUM TETRADECYL SULFATE.**—For monograph see the chapter on sclerosing agents.

### Cationic

The neutral salts (hydrochlorides, etc.) of bases of high molecular weight comprise this group. They include fatty amine salts, quaternary ammonium compounds or alkyl pyridinium compounds and the so-called basic dyes such as the polyphenylmethane antiseptics (brilliant green, auramine and crystal violet) and the acridine antiseptics (proflavine and acriflavine hydrochloride). The dyes are discussed in another section of this chapter.

Cationic surface-active agents bear positive electrical charges on their hydrophobic groups. Cationic agents are effective against both gram-positive and gram-negative organisms but higher concentrations are required to kill the latter type. The antibacterial action

of these agents increases as the pH is increased. Cationic agents possess a low order of toxicity although some of the fatty salts appear to be primary irritants or skin sensitizers.

Since the antibacterial action of cationic compounds is opposed by that of anionic agents (soap in concentrations as low as 0.1 per cent decreases the action), their application to the intact skin to be prepared for surgery must be preceded by thorough rinsing of the soap-cleaned areas, first with water and then with 70 per cent alcohol. The use of alcohol diminishes the ionization of ordinary soap solution, so that the inactivating chemical union of soap with the disinfectant is prevented.

Cationic detergents are not virucidal, sporicidal or fungicidal and cannot be relied upon for sterilization of surgical instruments and heat-labile articles. They may, however, be used to preserve the sterility of articles during storage.

The "quaternary ammonium compounds" are synthetic salts of organic, nitrogen-containing compounds. The properties of the two types are similar: (1) The four hydrogens of the ammonium radical,  $[NH_4]^+$ , are replaced by alkyl or aryl groups and (2) the nitrogen of heterocyclic radicals is completely alkylated or arylated.

The antibacterial properties of these compounds are due to their chemical reactivity and to their adsorbability; the same properties often account for their failure as germicides. They are completely adsorbed by charcoal and to a lesser degree by agar. Due to this high degree of adsorption on the bacterial wall, test methods which incorporate a neutralizing or desorbing substance are employed for determining the antibacterial action of these compounds. Methods which do not include this procedure measure only bacteriostatic properties of the agent. Quaternary ammonium compounds combine readily with proteins and therefore are less efficient in the presence of serum and other organic matter. Some phosphates diminish their effectiveness; fats affect them physically. The many quaternary ammonium compounds that have been synthesized vary in their antibacterial action; some are inefficient as disinfectants and sanitizers.

The logarithmic survival curve of bacteria subjected to the action of quaternary ammonium compounds is straight only for the killing of the first 99.9 per cent; after that, the death rate decreases and the last survivors display marked resistance.

Certain limitations are emphasized when the quaternary ammonium compounds are utilized as skin disinfectants because they form a film on the skin under which bacteria remain viable. The film is moderately resistant to mechanical trauma; its inner surface possesses little antibacterial action whereas the outer surface exerts considerable action. Disinfection of the surgeon's hands in gloveless surgery depends upon the mechanical stability of the film and upon the neutralizing effect of tissue fluids and blood. Sterilization of the operative field and the incision itself by these agents is doubtful.

The quaternaries have been recommended as satisfactory sanitizing rinses for reduction of the bacterial flora on eating and

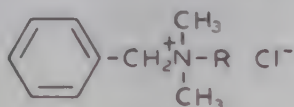


drinking utensils and dairy equipment, provided thorough mechanical cleansing and removal of anionic detergents precedes the rinse. Rise in temperature increases the efficiency of these and other disinfectants.

Strains of *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* are particularly resistant to these agents. Bacterial spores remain viable even after prolonged contact with solutions of the quaternaries. Utility of these agents for combating bacterial and fungal infections is not established.

In the concentrations commonly employed the quaternary ammonium salts are not toxic to animals.

**BENZALKONIUM CHLORIDE-U.S.P.—Zephiran Chloride** (WINTHROP-STEARNs).—Alkylbenzyltrimethylammonium chloride.—“Benzalkonium Chloride is a mixture of alkylbenzyltrimethylammonium chlorides of the general formula,  $[C_6H_5CH_2N(CH_3)_2R]Cl$ , in which R represents a mixture of the alkyls from  $C_8H_{17}$  to  $C_{18}H_{37}$ . It contains, when calculated to the anhydrous basis, not less than 97 per cent and not more than 103 per cent of  $[C_6H_5CH_2N(CH_3)_2R]Cl$ .” U.S.P. The structural formula of benzalkonium chloride may be represented as follows:



**Physical Properties.**—Benzalkonium chloride occurs as a white or yellowish white, amorphous powder or in the form of gelatinous pieces. It has an aromatic odor and a very bitter taste. Its solution is slightly alkaline to litmus paper and strongly foams when shaken. It is very soluble in water, in alcohol or in acetone; it is almost insoluble in ether and is slightly soluble in benzene.

**Actions and Uses.**—Benzalkonium chloride properly diluted is an effective, noninjurious, surface disinfectant which is germicidal for many pathogenic nonsporulating bacteria and fungi after several minutes' exposure. Solutions of benzalkonium chloride have low surface tension and possess detergent, keratolytic and emulsifying actions, properties which assist penetration and wetting of tissue surfaces. Organic matter and anionic compounds rapidly reduce its activity.

Effective concentrations of benzalkonium chloride are emollient and of comparatively low toxicity. Rabbits tolerate from 3 to 5 cc. of a 1 per cent aqueous solution orally or 1.2 cc. per kilogram of body weight, administered subcutaneously or intraperitoneally. Application of various concentrations to the skin of these animals, shows that a 0.1 per cent solution is the highest concentration that may be allowed to remain in contact for 24 hours without producing irritation.

Benzalkonium chloride is suitable for general use in the prophylactic disinfection of the intact skin and mucous membranes and



in the treatment of superficial injuries and infected wounds. It is also used to preserve the sterility of surgical instruments and rubber articles during storage. To prevent corrosion 0.5 per cent sodium nitrite is added to benzalkonium chloride solutions for the storage of metal instruments.

**Dosage.**—Benzalkonium chloride tincture 1:1,000 (tinted or stainless) may be used for the preoperative disinfection of unbroken skin or treatment of superficial injuries. Benzalkonium chloride solutions 1:2,000 to 1:10,000 are employed for the preoperative disinfection of mucous membranes and denuded skin, from 1:2,000 to 1:5,000 for instillation and irrigation of the eye or vagina and from 1:5,000 to 1:10,000 for widely denuded surfaces. For urinary bladder and urethral irrigation an aqueous solution not stronger than 1:20,000 is recommended; for retention lavage of the bladder, a concentration not to exceed 1:40,000. For therapeutic disinfection of deep lacerations the undiluted 1:1,000 aqueous solution may be employed, but for the irrigation of infected deep wounds, concentrations should not exceed 1:3,000. For the treatment of infected widely denuded areas with wet dressings, the aqueous solution should be used in concentrations of 1:5,000 or weaker.

For the sterile storage of metallic instruments and rubber articles, benzalkonium chloride solution 1:1,000 is used. For the disinfection of operating room equipment a 1:5,000 concentration of the solution may be employed.

#### WINTHROP-STEARNES, INC.

**Solution Zephiran Chloride 1:1,000:** 240 cc. and 3.78 liter bottles. A solution containing 1 mg. of benzalkonium chloride in each cubic centimeter.

**Solution Zephiran Chloride 12.8% (Concentrate):** 118 cc. and 3.78 liter bottles. A solution containing 0.13 Gm. of benzalkonium chloride in each cubic centimeter, which may be diluted with water or isotonic salt solution before use.

**Tincture Zephiran Chloride 1:1,000 (Stainless):** 240 cc. and 3.78 liter bottles. An alcohol-acetone-aqueous solution containing 1 mg. of benzalkonium chloride in each cubic centimeter.

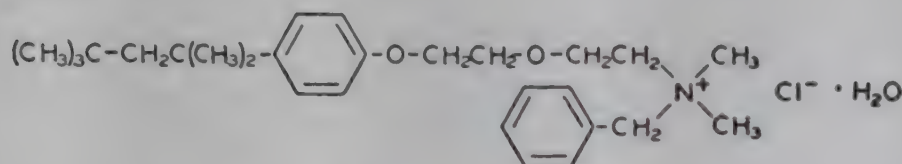
**Tincture Zephiran Chloride 1:1,000 (Tinted):** 240 cc. and 3.78 liter bottles. A red alcohol-acetone-aqueous solution containing 1 mg. of benzalkonium chloride in each cubic centimeter.

**Zephiran Tint:** 1.81 Gm. vials, D and C red No. 39, for use in the preparation of colored benzalkonium chloride solutions.

U. S. patents 2,108,765, 2,113,606 and 2,152,047. U. S. trademark 333,899.

**BENZETHONIUM CHLORIDE.**—Phemerol Chloride (PARKE, DAVIS). — Benzyldimethyl{2-[2-(*p*-1,1,3,3-tetramethylbutylphenoxy)ethoxy]ethyl}ammonium chloride monohydrate.—The struc-

tural formula of benzethonium chloride may be represented as follows:



**Physical Properties.**—Benzethonium chloride forms colorless, odorless crystals which are very bitter. It may be recrystallized from chloroform, by the addition of ether, in the form of very thin plates, which may be hexagonal. Mineral acids and many salt solutions precipitate benzethonium chloride from solutions more concentrated than 2 per cent, as an oil which crystallizes on drying and has the same properties as benzethonium chloride. A solution of benzethonium chloride yields a flocculent white precipitate with soap solutions. The pH of a 1 per cent solution of benzethonium chloride is between 4.8 and 5.5.

**Actions and Uses.**—Benzethonium chloride is a synthetic quaternary ammonium compound belonging to the cationic group of detergents. It inhibits metabolism and viability of commonly occurring nonsporulating bacteria. Both tinctures and aqueous solutions are used as general germicides and antiseptics. Soap and other anionic detergents, as well as organic matter, are incompatible with this agent.

**Dosage.**—Tincture benzethonium chloride 1:500 and aqueous solution benzethonium chloride 1:1,000 are used undiluted. For use in the nose and eye only the solution should be used, diluted with four parts of water.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Benzethonium Chloride:** Bulk; for manufacturing use.

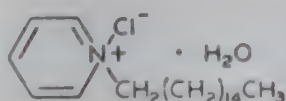
#### PARKE, DAVIS & COMPANY

**Solution Phemerol Chloride 1:1,000:** 480 cc. and 3.84 liter bottles.

**Tincture Phemerol Chloride 1:500:** 480 cc. and 3.84 liter bottles.

U. S. patent 2,115,250. U. S. trademark 305,545.

**CETYL PYRIDINIUM CHLORIDE.**—**Ceepryn Chloride (MERRELL).**—The monohydrate of the quaternary salt of pyridine and cetyl chloride. The structural formula of cetyl pyridinium chloride may be represented as follows:



**Physical Properties.**—Cetyl pyridinium chloride is a white powder with a slight odor. It melts between 77 and 83°. It is very soluble



in alcohol, chloroform and water and only very slightly soluble in benzene and ether. The pH of a 1 per cent solution is 6.0 to 7.0, as determined by the use of indicators (instruments with glass electrodes give variable results).

**Actions and Uses.**—Cetyl pyridinium chloride, a quaternary ammonium salt, is a cationic detergent that possesses useful surface-active as well as antiseptic properties against sensitive nonsporulating bacteria. It is employed in aqueous solution or tincture in appropriate dilutions for topical application in the preoperative disinfection of the intact skin and the prophylactic antisepsis of superficial minor wounds. It is also used by topical application or irrigation for therapeutic disinfection of accessible mucous membranes.

Cetyl pyridinium chloride is subject to the shortcomings of other cationic detergents employed as germicides in that its action is opposed by anionic detergents such as ordinary soap, may be reduced in the presence of serum and tissue fluids, and is not reliable against clostridial spores.

**Dosage.**—Intact skin may be prepared for surgery by scrubbing for 5 to 10 minutes with an aqueous solution of cetyl pyridinium chloride 1:100. When the conventional soap-alcohol-ether-germicide method is to be employed, 1:500 or 1:1,000 tincture dilutions may be used as the germicide if soap is completely removed before application. Similar dilutions of the tincture or a 1:1,000 aqueous solution may be used for topical application to minor lacerations and abrasions. For disinfection of delicate mucous membranes or extensive areas of exposed tissue, 1:5,000 to 1:10,000 solutions should be used.

#### THE WM. S. MERRELL COMPANY

**Concentrated Solution Ceepryn Chloride 10%:** 180 cc. and 3.78 liter bottles. An aqueous solution containing 0.1 Gm. of cetyl pyridinium chloride and 80 mg. of monobasic sodium phosphate in each cubic centimeter for the preparation of solutions and tinctures for external use.

**Isotonic Solution Ceepryn Chloride 1:1,000:** 480 cc. and 3.78 liter bottles. A solution containing 1 mg. of cetyl pyridinium chloride in each cubic centimeter which is made isotonic by addition of monobasic sodium phosphate and disodium phosphate.

**Tincture Ceepryn Chloride 1:200 (Tinted):** 480 cc. and 3.78 liter bottles. An alcohol-acetone-aqueous solution containing 5 mg. of cetyl pyridinium chloride in each cubic centimeter.

**Tincture Ceepryn Chloride 1:500 (Tinted):** 480 cc. and 3.78 liter bottles. An alcohol-acetone-aqueous solution containing 2 mg. of cetyl pyridinium chloride in each cubic centimeter.

U. S. patent 2,295,504. U. S. trademark 398,185.

**METHYLBENZETHONIUM CHLORIDE.** — Diaparene Chloride (HOMEMAKERS' PRODUCTS).—Benzyl dimethyl{2-[2-(*p*-1,1,3,3-tetramethylbutylcresoxy)ethoxy]ethyl}ammonium chloride. — The





## 5

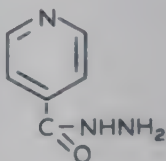
# Systemic Anti-Infectives

Systemic anti-infectives include therapeutic agents administered internally, orally or parenterally to combat infection. Thus the chapter includes antibacterial, antibiotic, antimalarial and antiprotozoan drugs as well as those effective in certain virus and fungus diseases. Some of the so-called urinary or intestinal antiseptics, though used principally for their local effect, are included because they are administered internally. Others that may be used, both locally and internally, are included in this chapter or the chapter on local anti-infectives on the basis of the principal method of application.

## ANTIBACTERIAL AGENTS

### Isonicotinic Acid Derivatives

**ISONIAZID.**—Niadrin (ENDO).—Nicozide (PREMO).—Nydrizid (SQUIBB).—Pyrizidin (NEPERA).—Rimifon (HOFFMANN-LAROCHE).—Tyvid (MERRELL).—Zinadon (KEITH-VICTOR).—Isonicotinic acid hydrazide.—The structural formula of isoniazid may be represented as follows:



**Physical Properties.**—Isoniazid is a white, odorless, crystalline powder. It melts between 170 and 173°. It is sparingly soluble in alcohol, very slightly soluble in benzene and ether and freely soluble in water. The pH of a 1 per cent solution is 5.5 to 6.5.

**Actions and Uses.**—Isoniazid is an antibacterial agent highly active in vitro against human, bovine and Calmette-Guérin bacillus strains of *Mycobacterium tuberculosis*. In vitro, it is effective at concentrations of 0.02 to 0.06 mcg. per milliliter; streptomycin is inhibitory at 0.52 mcg. per milliliter, while *p*-aminosalicylic acid is partially inhibitory at 200 mcg. per milliliter. Isoniazid is effective only against mycobacteria, except for some slight activity against *Trichophyton mentagrophytes* and certain other species of fungus. Clinically the drug may be used in tuberculosis for simultaneous administration with other tuberculostatic agents in patients for whom chemotherapy is indicated by present criteria. The drug may be employed alone in tuberculous patients who are already



hypersensitive to streptomycin or whose tubercle bacilli are resistant to the latter drug. Otherwise, combined therapy is preferable to the administration of isoniazid alone in order to avoid if possible the development of resistance to either agent, as this would decrease the chance of early response to chemotherapy, surgical treatment or both. Although the exact place of isoniazid in the chemotherapy of tuberculosis is still to be determined, so far it is considered to be of value in the pulmonary and renal forms of the disease, as well as in miliary tuberculosis, tuberculous meningitis and discharging "cold abscesses."

Isoniazid is almost completely absorbed from the digestive tract. In persons with normal renal function, from one-half to three-fourths of the amount ingested is recovered from the urine in 24 hours, and not more than 5 to 10 per cent of the drug appears in the feces. The peak concentration in the blood occurs 1 to 3 hours after oral administration, and the minimal detectable concentration of 0.4 mcg. per cubic centimeter persists for 6 to 24 hours following a single dose of 3 mg. per kilogram of body weight. This level is above the concentration necessary for *in vitro* tuberculostatic effects. The concentration in the saliva is comparable to that in the blood. The drug passes readily through the meningeal barrier and is well distributed in all of the various body fluids. There is no evidence that the drug accumulates in the tissues or that tolerance develops when administration of the recommended dosage is continued.

Intramuscular injection produces plasma concentrations approximately equal to those obtained with the same dosage administered orally. Following injection, the drug is somewhat more rapidly excreted in the urine. Transient, local pain at the site of injection may be encountered. Intramuscular injection of the drug is therapeutically equivalent to oral administration and should be employed whenever the latter route is not feasible, as in coma caused by tuberculous meningitis or during the early postoperative period following pulmonary resection. An injectable solution may also be employed topically for tuberculous empyema or effusion.

Experimental animal studies indicate a wide margin of safety between the effective and toxic doses of isoniazid. Toxic doses in animals produce reversible symptoms, which include anorexia, weight loss (from loss of appetite), liver damage and signs of central nervous system stimulation manifested by tremor, ataxia, rapid respiration, bradycardia and, in some instances, convulsions. In laboratory animals, phenobarbital diminishes the convulsive action of isoniazid and forced feeding has mitigated the hepatic damage produced by isoniazid in these animals. Toxic doses also produce some kidney damage in animals. Since isoniazid is excreted chiefly by the kidney, it should be given with caution and in the lowest recommended effective dose where renal damage is expected or known to exist. Renal tuberculosis should not be treated unless adequate facilities are available for estimating blood levels of isoniazid.

The toxic effects observed in human beings include vertigo, constipation, twitching of the lower extremities, drowsiness, head-



ache, hyperreflexia, dryness of the mouth and delay of the urinary stream. Toxicity has not been noted in patients receiving total daily doses of 5 mg. per kilogram of body weight who did not have existing convulsive disorders. Epilepsy or convulsions (in cases of meningitis) should be adequately controlled by appropriate anti-convulsant medication before and during isoniazid therapy.

**Dosage.**—Isoniazid is administered orally or intramuscularly in the recommended daily dosage of 3 to 5 mg. per kilogram of body weight, divided into equal doses every 12 hours. This dosage should be exceeded only with caution and when adequate facilities are available to detect toxic symptoms. In patients seriously ill, such as those suffering from tuberculous meningitis or miliary tuberculosis, it is advisable to use a daily dosage of 7 mg. per kilogram of weight for a period of 7 to 10 days, then to reduce this to the usual maximum total daily dosage. The dosage should be reduced when signs of a toxic central nervous system stimulation develop.

Isoniazid may be used concurrently with streptomycin or dihydrostreptomycin. Either of those drugs should be administered intermittently twice weekly or every 3 days in doses of 1 Gm. for adults or 20 mg. per kilogram of body weight for children, given intramuscularly. Concomitant use of isoniazid with daily 1 Gm. doses of a streptomycin drug should be restricted to acute forms of tuberculosis and limited to a period of 1 to 2 weeks until there is more information concerning the side effects that may result from this method of therapy.

For intramuscular injection, a solution containing 100 mg. per cubic centimeter should be administered so as to provide the same dosage as that indicated by the oral route. The same concentration can be applied topically in 10 cc. amounts three times weekly for the local treatment of tuberculous empyema or effusion.

#### AMERICAN PHARMACEUTICAL COMPANY

Tablets Isoniazid: 50 mg.

#### THE BOWMAN BROS. DRUG COMPANY

Tablets Isoniazid: 50 mg.

#### ENDO PRODUCTS, INC.

Tablets Niadrin: 50 and 100 mg.

U. S. trademark 398,543.

#### HOFFMANN-LAROCHE, INC.

Tablets Rimifon: 50 and 100 mg.

U. S. patent 2,596,069. U. S. trademark 563,939.

#### KEITH-VICTOR PHARMACAL COMPANY

Tablets Zinadon: 50 and 100 mg.

#### THE WM. S. MERRELL COMPANY

Tablets Tyvid: 50 mg.

NEPERA CHEMICAL COMPANY, INC.

Tablets Pyrizidin: 50 and 100 mg.

THE PANRAY CORPORATION

Tablets Isoniazid: 50 and 100 mg.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Nicozide: 50 and 100 mg.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

Capsules Nydrazid: 50 and 100 mg.

Solution Nydrazid (*Intramuscular*): 10 cc. vials. A solution containing 100 mg. of isoniazid in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

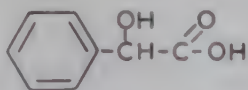
Syrup Nydrazid: 473 cc. bottles. A flavored syrup containing 10 mg. of isoniazid in each cubic centimeter. Preserved with 0.1 per cent of sodium benzoate.

Tablets Nydrazid: 50 and 100 mg.

U. S. trademark 562,900.

## Mandelic Acid Derivatives

**MANDELIC ACID-N.F.**—Racemic Mandelic Acid.—“Mandelic Acid, dried over sulfuric acid for 4 hours, contains not less than 99 per cent of  $C_8H_8O_3$ .” *N.F.* The structural formula of mandelic acid may be represented as follows:



**Physical Properties.**—Mandelic acid occurs as white crystals or crystalline powder. It is odorless or has a slight aromatic odor; it gradually darkens and decomposes on exposure to light. One gram dissolves in about 6.5 cc. of water at 25°; it is freely soluble in alcohol.

**Actions and Uses.**—Mandelic acid is a substance which is not metabolized; when administered by mouth, it is excreted unchanged in the urine. If the pH of the urine is kept at 5.5 or less, mandelic acid is bactericidal or bacteriostatic against *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis* and organisms of the Proteus, Pseudomonas, Alcaligenes, Salmonella and Shigella groups. The acidity should be controlled by frequent determinations of the pH. When the acidity is not reduced to pH 5.5 or less, other acidifying agents such as ammonium chloride, ammonium nitrate or nitrohydrochloric acid may be administered concurrently providing there are no contraindications. The ketogenic diet has also been employed to maintain urine acidity. Fluid intake should not exceed

1,200 cc. daily. It is usually unnecessary and inadvisable to continue mandelic acid therapy longer than 12 to 14 days, as renal irritation may ensue. Nausea, diarrhea, dysuria and hematuria also occur occasionally, requiring reduction in dosage or interruption of therapy. Mandelic acid should not be administered in the presence of renal insufficiency, as an inadequate concentration is obtained in the urine; renal irritation and serious acidosis may result from retention of the acid.

**Dosage.**—The usual dosage is 3 Gm. four times a day of either the free acid or the sodium or ammonium salt. An additional acidifying agent is usually required when the sodium salt is employed.

#### MALLINCKRODT CHEMICAL WORKS

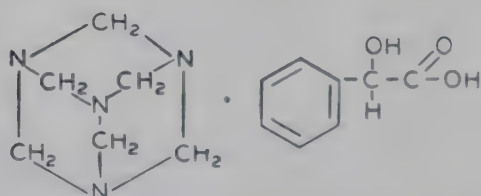
**Powder Mandelic Acid:** Bulk; 454 Gm. containers for compounding use.

#### MERCK & COMPANY, INC.

**Powder Mandelic Acid:** Bulk; 113 and 453 Gm. bottles for compounding use.

### Methenamine Compounds

**METHENAMINE MANDELATE.**—Mandelamine (NEPERA).—The salt obtained from the reaction of equimolecular amounts of methenamine-U.S.P. and mandelic acid-N.F. containing 48 per cent methenamine and 52 per cent mandelic acid by weight. The structural formula of methenamine mandelate may be represented as follows:



**Physical Properties.**—Methenamine mandelate is a white, crystalline powder with a sour taste and practically no odor. It melts between 127 and 130°. It is very soluble in water. One part of methenamine mandelate is soluble in about 10 ml. of alcohol, 20 ml. of chloroform and 350 ml. of ether. The pH of a 1 per cent solution is between 4.2 and 4.4.

**Actions and Uses.**—Methenamine mandelate combines the actions of two established urinary antiseptics, methenamine and mandelic acid. The compound acts to some extent as an acidifying agent. However, in those infections caused by urea-splitting bacteria, preliminary acidification of the urine over a period of 24 to 36 hours prior to beginning therapy is essential to provide a urinary pH satisfactory for effective action of the compound. The combination has the theoretic advantage that it is effective with smaller amounts



of mandelic acid and may thus avoid the nausea and vomiting occasionally attributed to the use of mandelic acid alone.

Methenamine mandelate is useful as an adjunct for the treatment of pyelitis, pyelonephritis, cystitis and infections accompanying a neurogenic bladder. It is effective against the following organisms commonly encountered in urinary tract infections: *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus albus* and certain streptococci. *Proteus vulgaris* is usually resistant, but not more so than to most other commonly employed antibacterial agents. Comparative studies of the bacteriostatic and bactericidal action of methenamine mandelate indicate that its effectiveness is of approximately the same order as that of the sulfonamide drugs. It is sometimes effective when drug resistance to other agents occurs with certain otherwise susceptible bacterial strains.

Methenamine mandelate is seldom associated with untoward effects; in therapeutically effective amounts, gastric disturbance is infrequent and other toxic manifestations are relatively rare. It is contraindicated in the presence of renal insufficiency.

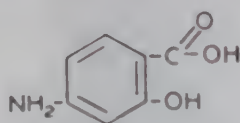
**Dosage.**—Methenamine mandelate is administered orally. The average dose for adults is 0.75 to 1 Gm. three times daily; for children over 5 years of age, 0.25 Gm. three times daily; for infants less than 1 year of age, 0.25 Gm. twice daily.

NEPERA CHEMICAL COMPANY, INC.

Tablets Mandelamine: 0.25 Gm. enteric coated.

U. S. patent 2,124,321. U. S. trademark 347,322.

**p-AMINOSALICYLIC ACID.**—**Para-Pas** (GOLD LEAF).—**Parasal** (PANRAY).—**Propasa** (SHARP & DOHME).—The structural formula for *p*-aminosalicylic acid may be represented as follows:



**Physical Properties.**—*p*-Aminosalicylic acid is a white or nearly white bulky powder which is odorless or has a slight acetous odor. It melts with decomposition between 135 and 140°. One part is soluble in 21 parts of alcohol and in 500 parts of water. At 25°, 0.2 Gm. dissolves in 100 ml. of water and 4.75 Gm. dissolves in 100 ml. of alcohol. One gram dissolves in 10 ml. of 10 per cent sodium bicarbonate to give a clear solution with no more than a faint yellow color. A saturated aqueous solution has a pH between 3.2 and 3.7.

**Actions and Uses.**—*p*-Aminosalicylic acid has in vitro and in vivo action against the tubercle bacillus, although it is less potent than the streptomycins. It is used principally as a supplement to these antibiotics, not only because it may produce some addition of effects, but also because the combination may postpone the development of bacterial resistance. *p*-Aminosalicylic acid may be indicated alone in tuberculous infections in which the bacilli have

become resistant to streptomycin and dihydrostreptomycin or where, for any reason, these antibiotics may be contraindicated. Resistance to *p*-aminosalicylic acid usually develops slowly. *p*-Aminosalicylic acid alone may be indicated, also, in infections which are deeply entrenched, especially when surgery is anticipated later and it is desirable to reserve the streptomycin drugs for that time.

The drug is well absorbed from the alimentary tract, producing blood levels which are usually maintained for 4 hours. Excretion in the urine is rapid and nearly complete. Epigastric discomfort, anorexia, nausea and vomiting are frequently troublesome toxic manifestations. Occasionally soft stools or, less frequently, diarrhea occurs. In other respects the drug has only rarely been harmful to human beings, but dermatoses and drug fever have been reported. Small initial doses; smaller, more frequent subsequent doses; simultaneous administration of 5 to 10 cc. of aluminum hydroxide gel, and the routine administration with meals may limit the gastrointestinal disturbances.

**Dosage.**—*p*-Aminosalicylic acid may be given in the form of tablets or capsules, coated granules or in solution. The recommended daily dose is 8 to 16 Gm., given orally in four or more doses.

#### AMERICAN PHARMACEUTICAL COMPANY

Powder Para-Aminosalicylic Acid: 454 Gm. bottles.

Tablets Para-Aminosalicylic Acid: 0.5 Gm. plain and specially coated brown.

#### CHEMO PURO MANUFACTURING CORPORATION

Powder Para-Aminosalicylic Acid: Bulk; for manufacturing use.

#### GOLD LEAF PHARMACAL COMPANY, INC.

Powder Para-Pas: 113.4 Gm., 226.7 Gm., 454 Gm. and 2.27 Kg. bottles, and 11.3 and 22.7 Kg. drums for compounding use.

Tablets Para-Pas: 0.5 Gm.

#### HEXAGON LABORATORIES, INC.

Powder Para-Aminosalicylic Acid: Bulk; for manufacturing use.

#### MERCK & COMPANY, INC.

Powder Para-Aminosalicylic Acid: 50 and 500 Gm. bottles; 2.5, 22.7 and 45.4 Kg. fiber drums (for manufacturing use only).

#### THE PANRAY CORPORATION

Powder Parasal: 113.4, 226.8 and 453.6 Gm. bottles. Bulk, 11.34 and 22.68 Kg. drums for compounding use.

Tablets Parasal: 0.5 Gm.

U. S. trademark 585,718.

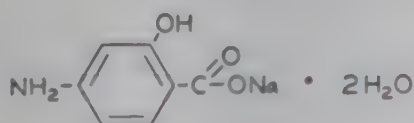
PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets *p*-Aminosalicylic Acid: 0.5 Gm.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Effervescent Tablets Propasa:** 1 Gm. Each tablet contains 1 Gm. of *p*-aminosalicylic acid and 0.7 Gm. of sodium bicarbonate. When dissolved in water, each tablet yields 1.38 Gm. of sodium *p*-aminosalicylate.

**SODIUM *p*-AMINOSALICYLATE.**—**Para-Pas Sodium (GOLD LEAF).**—**Parasal Sodium (PANRAY).**—**Pasara Sodium (SMITH-DORSEY).**—**Pasem Sodium (MASSENGILL).**—**Pasmed Sodium (INTERMEDICO).**—The structural formula for sodium *p*-aminosalicylate may be represented as follows:



**Physical Properties.**—Sodium *p*-aminosalicylate is a white to pale yellow, practically odorless, crystalline powder. It is freely soluble in water, sparingly soluble in alcohol and practically insoluble in ether. One gram dissolves in 50 ml. of water to give a clear solution which is colorless or nearly so. The solution has a pH between 7.0 and 7.5.

**Actions and Uses.**—See the monograph on *p*-aminosalicylic acid.

**Dosage.**—3 Gm. five times daily for a total dose of 15 Gm. every 24 hours. The duration of treatment is the same as with *p*-aminosalicylic acid.

AMERICAN PHARMACEUTICAL COMPANY

Powder Sodium Para-Aminosalicylate: 454 Gm. bottles.

Tablets Sodium Para-Aminosalicylate: 0.5 Gm.

CHEMO PURO MANUFACTURING CORPORATION

Powder Sodium Para-Aminosalicylate: Bulk; for manufacturing use.

GOLD LEAF PHARMACAL COMPANY, INC.

Powder Para-Pas Sodium: 113.4 Gm., 226.7 Gm., 454 Gm. and 2.27 Kg. bottles, and 11.3 and 22.7 Kg. drums for compounding use.

Tablets Para-Pas Sodium: 0.69 Gm.

HEXAGON LABORATORIES, INC.

Powder Sodium Para-Aminosalicylate: Bulk; for manufacturing use.

INTERMEDICO CORPORATION

Tablets Pasmed Sodium: 0.5 Gm.



S. E. MASSENGILL COMPANY

Capsules Fasem Sodium: 0.5 Gm.

MERCK & COMPANY, INC.

Powder Sodium Para-Aminosalicylate: 500 Gm. bottles and 11.35 and 45.4 Kg. fiber drums; for manufacturing use.

THE PANRAY CORPORATION

Powder Parasal Sodium: 113.4, 226.8 and 453.6 Gm. bottles. Bulk; 11.34 and 22.68 Kg. drums for compounding use.

Tablets Parasal Sodium: 0.69 Gm.

U. S. trademark 585,718.

PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Sodium *p*-Aminosalicylate: 0.5 Gm.

SMITH-DORSEY, DIVISION OF THE WANDER COMPANY

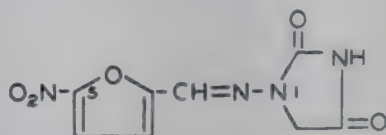
Capsules Pasara Sodium: 0.5 Gm.

Powder Pasara Sodium: 454 Gm. bottles and 11.34 Kg. containers.

Tablets Pasara Sodium: 0.5 Gm.

### Nitrofuran Derivatives

**NITROFURANTOIN.**—Furadantin (EATON).—N-(5-Nitro-2-furfurylidene)-1-aminohydantoin.—The structural formula of nitrofurantoin may be represented as follows:



**Physical Properties.**—Nitrofurantoin is a yellow, bitter powder with a slight odor, which decomposes at 258 to 262°. It is very slightly soluble in alcohol and practically insoluble in ether and water.

**Actions and Uses.**—Nitrofurantoin, a nitrofuran derivative, exhibits a wide spectrum of antibacterial activity against both gram-positive and gram-negative micro-organisms. It is both bacteriostatic and bactericidal to the majority of strains of *Escherichia coli*, *Micrococcus* (*Staphylococcus*) *pyogenes albus* and *aureus*, *Streptococcus pyogenes*, *Aerobacter aerogenes* and *Paracolonobacterium* species. The drug is less effective against *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Alcaligenes faecalis* and *Corynebacterium* species; many strains of these organisms may be resistant to it; however, bacterial resistance to other anti-infective agents is not usually accompanied by increase in resistance of the organisms to nitrofurantoin. The drug does not inhibit fungi or viruses.

Nitrofurantoin is useful by oral administration for the treatment of bacterial infections of the urinary tract and is indicated in pyelonephritis, pyelitis and cystitis caused by bacteria sensitive to the drug. It is not intended to replace surgery when mechanical obstruction or stasis is present. Following oral administration, between 40 to 50 per cent is excreted unchanged in the urine. The remainder is apparently catabolized by various body tissues into inactive, brownish compounds that may tint the urine. Only negligible amounts of the drug are recovered from the feces. Urinary excretion is sufficiently rapid to require administration of the drug at 4-hour to 6-hour intervals to maintain antibacterial concentration. The low oral dosage necessary to maintain an effective urinary concentration is not associated with detectable blood levels. The high solubility of nitrofurantoin, even in acid urine, and the low dosage required diminish the likelihood of crystalluria.

Nitrofurantoin has a low toxicity. With oral administration, it occasionally produces nausea and emesis; however, these reactions may be obviated by slight reduction in dosage. An occasional case of sensitization has been noted, consisting of a diffuse, erythematous, maculopapular eruption of the skin. This has been controlled readily by discontinuing administration of the drug. Animal studies, using large doses administered over a prolonged period, have revealed a decrease in the maturation of spermatozoa, but this effect is reversible following discontinuance of the drug. Until more is known concerning its long-term effects, blood cell studies should be made during therapy. Frequent or prolonged treatment is not advised until the drug has received more widespread study. It is contraindicated otherwise in the presence of anuria, oliguria or severe renal damage.

**Dosage.**—Nitrofurantoin is administered orally in an average total daily dosage of 5 to 8 mg. per kilogram (2.2 to 3.6 mg. per pound) of body weight. One fourth of this amount is administered four times daily—with each meal and with food at bedtime, to prevent or minimize nausea. For refractory infections caused by organisms such as *Proteus* and *Pseudomonas* species, the total daily dosage may be increased to a maximum of 10 mg. per kilogram (4.5 mg. per pound) of body weight. If nausea is severe, the dosage may be reduced. Medication should be continued for at least 3 days after sterility of the urine is achieved.

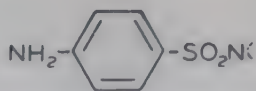
EATON LABORATORIES, INC.

**Tablets Furadantin:** 50 and 100 mg.

U. S. patent 2,610,181. U. S. trademark 569,968.

## Sulfonamide Compounds

The group of compounds referred to as sulfonamides contain in common the chemical group  $\text{—SO}_2\text{N}<$ . The therapeutically active members of this group which have been accepted by the Council are derivatives of sulfanilamide and are characterized by the group:



They may, in addition, carry a single substituent on the *p*-amino group.

The major effect of the sulfonamides as a group is to prevent synthesis by bacteria of pteroyl compounds. Pteroyl compounds are required by many species as growth factors. Sulfonamide therapy must be administered in dosages which will maintain concentrations sufficient to prevent the utilization of available *p*-aminobenzoic acid in the body. Insufficient therapy may result in an increase of resistant pathogenic forms. High concentrations may be bactericidal to susceptible invading organisms, but the major effect of sulfonamides upon micro-organisms is usually bacteriostatic. The antisulfonamide action of *p*-aminobenzoic acid is of special importance because many local anesthetics (procaine is a good example) are esters of *p*-aminobenzoic acid and are partly metabolized to the parent substance when injected into the tissues.

The choice of the sulfonamide compound to be used in the control of known infections should be based on bacteriologic diagnosis, knowledge of the experimental therapeutic value of these drugs, their pharmacologic properties in man, their clinical efficacy and finally, the variety, frequency and severity of the toxic reactions which each may produce.

Sulfonamides should not be used for the treatment of anaerobic streptococcic infections, enterococcic infections, rheumatoid arthritis, active rheumatic fever, subacute bacterial endocarditis, tularemia, undulant fever, tuberculosis, lymphogranuloma inguinale, the common cold, measles, influenza, pemphigus and a number of other infections. If there is an antibiotic which is effective for the treatment of a given infection, it usually should be employed in moderate or severe cases, either alone or in conjunction with a therapeutically active sulfonamide.

Experience gained in World War II indicates that the use of crystalline sulfonamides and of sulfonamide ointments, creams and lotions as topical agents was not successful in the management of wound infection, or in treatment of infections of the skin or mucous membrane. Use of sulfonamides as topical applications in wounds, burns and superficial infections is contraindicated, with the possible exception of ophthalmic application of sodium sulfacetamide and sulfisoxazole diethanolamine.

**Toxicity.**—Sulfonamide compounds produce many and varied toxic reactions. Hence patients who are being treated with these drugs should be examined at frequent intervals in order that the early signs of toxicity may be noted and the drug stopped.

The sulfonamides currently recommended produce fewer toxic reactions than did sulfanilamide, sulfapyridine or sulfathiazole. Nausea, vomiting, dizziness and cyanosis are uncommon and acidosis does not occur. Mental disturbances and acute psychoses have been observed in patients given one or a mixture of the pyrimidine derivatives.



Mild peripheral neuritis, drug fever, skin rashes of many morphologic types, injection of the conjunctiva and sclera, petechiae and purpura have occurred. Acute toxic hepatitis is uncommon but has been reported; acute hemolytic anemia is rare. Granulocytopenia has been observed early and late in the course of treatment with pyrimidine derivatives, and agranulocytosis occurs most frequently between the tenth and twenty-first days of therapy. Microscopic and gross hematuria with or without crystalluria may occur during treatment with the pyrimidine derivatives, especially when the patient's intake of fluids has been low. Complete cessation of renal function, beginning with oliguria and progressing to anuria accompanied by azotemia, is the most common serious toxic reaction to the individual pyrimidine derivatives; it occurs less frequently when mixtures of the pyrimidine derivatives are administered. Because of the possibility that renal lesions may be produced, fluids adequate to produce a daily urinary output of at least 1,000 cc., should be given to patients receiving any pyrimidine derivatives. Alkalization of the urine during treatment with sulfadiazine, sulfamerazine, and/or sulfamethazine, decreases the likelihood of renal complications. When serious toxic reactions develop, the sulfonamide should be stopped and fluids forced in order that the drug may be eliminated as rapidly as possible. However, when oliguria or anuria is present, fluids should not be administered to the point of producing edema. In order to avoid photosensitization, all patients receiving sulfonamides should be kept out of the sun, and should not receive ultraviolet radiation.

When sulfonamide drugs are being used it is always desirable to determine the values of the sulfonamides in the blood and body fluids at frequent intervals by the method described by Bratton and Marshall (*J. Biol. Chem.* 128:537 [May] 1939).

**Sulfonamide Sodium Salts.**—Solutions of sulfonamide sodium salts in distilled water are strongly alkaline and have pH ranges from 9 to 11. When solutions of these drugs are injected intravenously the sodium ions are promptly split off, leaving the sulfonamide compound in the circulating blood. Hence, in the final analysis, sulfonamide sodium salts represent vehicles for introducing the slightly soluble parent compounds into the body. The preferred method of administering the sodium salts of sulfonamide compounds is intravenous injection as 5 per cent solutions in sterile pyrogen-free distilled water or sterile pyrogen-free isotonic sodium chloride solution.

The intravenous injection of 5 per cent solutions of the sodium salts of the sulfonamide compounds should be carried out carefully because these solutions, being highly alkaline, are irritating to the tissues and, if they are permitted to leak outside the vein, may cause necrosis of the tissues with sloughing. Solutions of such strength should never be given by the intrathecal route because of the danger of producing a chemical necrosis of the tissues. It has been shown that 0.3 to 0.7 per cent solutions of the sodium salts of the sulfonamide compounds can be safely administered in saline or isotonic Ringer's solution by the subcutaneous route. However, the

general use of this route is not advised unless the drugs cannot be administered intravenously.

The use of solutions of the sodium salts of sulfonamide compounds is indicated in severe infection in which it is desired to obtain promptly adequate blood concentrations of these drugs, for patients who by reason of disturbances of the gastro-intestinal tract, such as vomiting, are not obtaining proper concentrations of these drugs when they are given orally and, finally, for patients in whom the absorption of these drugs is poor or whose rate of conjugation is such that adequate concentrations cannot be obtained in the blood and tissues by other routes of administration.

With the exception of patients ill with severe infections, and those to whom these drugs cannot be given by the oral route, it is rarely necessary to administer intravenous injections of solution of the sodium salts of the sulfonamides more than once or twice. Frequent and repeated injections of the drug are not advised because they tend to produce thrombosis of the veins. Whenever possible, instead of continuing administration of solution of sodium salt of the sulfonamide compounds by the parenteral route, administration of the parent drug by the oral route should be commenced.

Aside from the damage to tissues which may result from the careless administration of the sodium salts of these sulfonamides by the intravenous route, the toxic reactions noted in the course of their administration are those which occur when the parent sulfonamide is administered by the oral route.

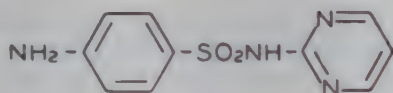
### *Pyrimidine Derivatives*

When sulfadiazine is administered orally, its absorption from the gastro-intestinal tract is slower and less complete than that of sulfanilamide. Sulfamethazine resembles sulfadiazine in respect to absorption, but sulfamerazine is absorbed more rapidly and completely than either. As sulfamerazine is excreted more slowly than sulfadiazine or sulfamethazine, smaller doses produce blood concentrations comparable to those obtained with either of the other two pyrimidine derivatives. All three of these agents are excreted primarily in the urine, where they are found in the free and conjugated forms. The renal clearance of sulfamethazine is similar to that of sulfamerazine and about half that of sulfadiazine, and when renal function is subnormal, they accumulate in the blood. Acetylated sulfamerazine is the most soluble of the three drugs, but sulfamethazine, when absorbed, is conjugated to the acetyl derivatives more easily than are the other two compounds. All three pass over into the spinal fluid in fair concentrations, and the concentrations increase when the meninges are inflamed. None of them passes into the body water as readily as does sulfanilamide, but the concentrations in pleural and abdominal fluids are 50 to 80 per cent of those in the blood. Adequate blood concentrations are obtained easily with all three of the drugs. Each is bound to the blood proteins to a different degree, sulfamethazine having the highest binding power. All three pyrimidine derivatives penetrate the red blood cells.



Sulfadiazine, sulfamerazine and sulfamethazine, singly or in mixtures, are effective in hemolytic streptococcic infections caused by Lancefield's Group A organisms and in pneumococcic, meningococcic and staphylococcic infections. Urinary tract infections produced by *E. coli*, *A. aerogenes*, *B. proteus*, *Ps. aeruginosa* and systemic infections caused by *Kl. pneumoniae* or *H. influenzae* may also respond. These sulfonamides are also beneficial in the treatment of bacillary dysentery and early trachoma and may have some effect in lymphogranuloma venereum, follicular conjunctivitis and mollusum contagiosum. One of the diazines may be used also in chancroid and for peroral prophylaxis of rheumatic fever. For carriers of meningococcus, it is usually sufficient to administer 2 Gm. of sulfadiazine per day for 2 days. Actinomycosis or gas gangrene may be treated with sulfadiazine, sulfamerazine or sulfamethazine in conjunction with a potent antibiotic.

**SULFADIAZINE-U.S.P.** — 2-Sulfanilamidopyrimidine. —  $N^1-2$  — Pyrimidylsulfanilamide.—“Sulfadiazine, dried at  $105^\circ$  for 2 hours, contains not less than 99 per cent of  $C_{10}H_{10}N_4O_2S$ .” *U.S.P.* The structural formula of sulfadiazine may be represented as follows:



**Physical Properties.**—Sulfadiazine occurs as a white, odorless, tasteless, crystalline powder. It may be recrystallized from hot water to yield long, flat needles. It is soluble in both alkaline and mineral acid solutions; sparingly soluble in alcohol, acetone and water; insoluble in ether and chloroform.

**Actions and Uses.**—See the general statement on sulfonamides and on pyrimidine derivatives.

**Dosage.**—Sulfadiazine is practically insoluble and hence must be administered by the oral route. In adults suffering from pneumococcic pneumonia, severe hemolytic streptococcus infections, severe staphylococcic infections or meningococcic meningitis, the initial dose should be 0.1 Gm. per kilogram of body weight. Then, if the patient is suffering from pneumococcic pneumonia, 1 Gm. should be given every 4 hours day and night until the temperature has been normal for 72 hours. The drug may then be withdrawn. In severe streptococcic, staphylococcic and meningococcic infections, subsequent doses after the initial doses are 1 to 1.5 Gm. every 4 hours day and night until the temperature has been normal for 5 to 7 days. At this time the drug may be either stopped or continued in smaller doses until the complete recovery of the patient is assured.

In children suffering from pneumonia the initial oral dose should be based on 0.1 to 0.15 Gm. per kilogram of body weight, and subsequent doses of one-fourth of the initial dose should be given at intervals of 6 hours until the temperature has been normal for at least 48 hours. In severe streptococcic, staphylococcic or meningococcic infections in children the drug should be continued until



5 to 7 days of normal temperature have elapsed. Then it may be discontinued or, if necessary, continued in smaller doses until a cure is effected.

In mild or moderately severe hemolytic streptococcus infections, the dosage suggested is an initial oral dose of 0.05 Gm. per kilogram of body weight, followed by one-third of the initial dose given every 4 hours day and night by mouth until the temperature has been normal for 3 to 5 days. All of the above dosages should be controlled if possible by determination at frequent intervals of the concentration of the drug in the blood (see Bratton and Marshall method under *Toxicity* in the general statement on sulfonamide compounds). In severe streptococcal, staphylococcal, meningococcal or Friedländer's bacillus infections, it is necessary during the febrile period to obtain and maintain concentrations of approximately 15 mg. of sulfadiazine per 100 cc. in the patients' blood; it is rarely necessary or advisable to exceed this concentration. In mild or moderately severe streptococcus infections, concentrations of 5 to 10 mg. of the drug per 100 cc. of blood are usually satisfactory. In acute gonococcus urethritis in adults, the initial dose is 4 Gm., to be followed by 1 Gm. every 6 hours for 5 days.

There may be a high incidence of oliguria, hematuria and anuria following sulfadiazine therapy under conditions where the output of urine cannot be maintained above 600 or 800 cc. per day, as in tropical climates or where a shortage of water exists. It is recommended that where such complications are encountered, an initial dose of 4 Gm. of sodium bicarbonate together with the initial dose of sulfadiazine be administered, followed by 2 Gm. of sodium bicarbonate every 4 hours regardless of the dosage of sulfadiazine being employed. In the management of complications resulting from the toxic action of sulfadiazine on the kidneys, the administration of even larger doses of alkali, such as 3 or 4 Gm. every 4 hours, may be helpful.

#### ABBOTT LABORATORIES

**Dulcet Tablets Sulfadiazine:** 0.15 and 0.3 Gm.  
U. S. trademark 500,527.

**Powder Sulfadiazine:** 113 and 454 Gm. bottles.

**Tablets Sulfadiazine:** 0.5 Gm.

#### AMERICAN PHARMACEUTICAL COMPANY, INC.

**Tablets Sulfadiazine:** 0.5 Gm.

#### THE BOWMAN BROS. DRUG COMPANY

**Tablets Sulfadiazine:** 0.5 Gm.

**Hexett Tablets Sulfadiazine:** 65 mg.

#### BOYLE & COMPANY

**Tablets Sulfadiazine:** 0.5 Gm.

BREWER & COMPANY, INC.

Tablets Sulfadiazine: 0.5 Gm.

BUFFINGTON'S, INC.

Tablets Sulfadiazine: 0.5 Gm.

COLE CHEMICAL COMPANY

Tablets Sulfadiazine: 0.5 Gm.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Powder Sulfadiazine: 113 and 454 Gm. packages.

Tablets Sulfadiazine: 0.5 Gm.

ELI LILLY & COMPANY

Tablets Sulfadiazine: 65 mg. and 0.5 Gm.

MALLARD, INC.

Tablets Sulfadiazine: 0.5 Gm.

MCNEIL LABORATORIES

Liquoid Sulfadiazine: 120 and 480 cc. bottles. A suspension containing 0.1 Gm. of sulfadiazine in each cubic centimeter.

Tablets Sulfadiazine: 0.5 Gm.

THE WM. S. MERRELL COMPANY

Tablets Sulfadiazine: 0.5 Gm.

E. S. MILLER LABORATORIES, INC.

Tablets Sulfadiazine: 0.5 Gm.

PARKE, DAVIS & COMPANY

Tablets Sulfadiazine: 0.5 Gm.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Sulfadiazine: 0.5 Gm.

PITMAN-MOORE COMPANY

Magmoid Sulfadiazine: 360 cc. and 3.84 liter bottles. A suspension containing 0.1 Gm. of sulfadiazine in each cubic centimeter. Preserved with 0.25 per cent benzoic acid.

REXALL DRUG COMPANY

Tablets Sulfadiazine: 0.5 Gm.

WILLIAM H. RORER, INC.

Tablets Sulfadiazine: 0.5 Gm.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

Tablets Sulfadiazine: 0.5 Gm.

U. S. patents 2,407, 966 and 2,410,793.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

Tablets Sulfadiazine: 0.5 Gm.

MARVIN R. THOMPSON, INC.

Suspension Sulfadiazine with Sodium Lactate: 473 cc. and 3.78 liter bottles. A liquid suspension containing 0.1 Gm. of sulfadiazine and 0.3 Gm. of sodium lactate in each cubic centimeter.

U. S. patent 2,460,437.

THE UPJOHN COMPANY

Tablets Sulfadiazine: 0.5 Gm.

THE VALE CHEMICAL COMPANY, INC.

Tablets Sulfadiazine: 0.5 Gm.

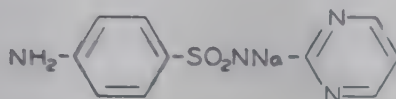
VANPELT & BROWN, INC.

Tablets Sulfadiazine: 0.5 Gm.

WINTHROP-STEARNs, INC.

Tablets Sulfadiazine: 0.5 Gm.

**SULFADIAZINE SODIUM-U.S.P.**—The sodium salt of 2-sulfanilamidopyrimidine.—“Sulfadiazine Sodium, dried at 105° for 2 hours, contains not less than 99 per cent of  $C_{10}H_9N_4NaO_2S$ .” *U.S.P.* The structural formula of sulfadiazine sodium may be represented as follows:



**Physical Properties.**—Sulfadiazine sodium occurs as a white, odorless powder, having a bitter taste. It is very soluble in water. Aqueous solutions may absorb sufficient carbon dioxide to cause precipitation of sulfadiazine. Sulfadiazine sodium is not hygroscopic at 25° if the relative humidity does not exceed 50 per cent.

**Actions and Uses.**—See the general statement on sulfonamides and on pyrimidine derivatives.

**Dosage.**—The usual initial dose for patients who are severely ill with infections which are susceptible to this drug is based on 0.1 Gm. per kilogram of body weight, up to 50 Kg. of body weight. This dose is made up as a 5 per cent solution in sterile distilled water or isotonic solution of sodium chloride. It is injected into a vein. Regardless of the weight of the patient, it is best not to exceed a total initial dosage of 5 Gm. of sulfadiazine sodium. It is always advisable to continue therapy by the administration of sulfadiazine by the oral route, but, if this is impossible, subsequent doses of sulfadiazine sodium should be based on 0.03 to 0.05 Gm. of sodium sulfadiazine per kilogram of body weight, in a 5 per cent solution in distilled water, administered by the intravenous route at 6-hour to 8-hour intervals.



When solutions of sulfadiazine sodium are being used as the sole therapy, daily determinations of the concentration of the drug in the blood should be made in order to prevent accumulation of inordinately high levels of the drug in the blood. The dosages suggested are applicable to children as well as adults.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

**Solution Sodium Sulfadiazine 25%:** 10 cc. ampuls. Each cubic centimeter contains 0.25 Gm. of sodium sulfadiazine in distilled water. Preserved with 0.1 per cent sodium thiosulfate.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Powder Sodium Sulfadiazine (Sterile):** 5 Gm. vials.

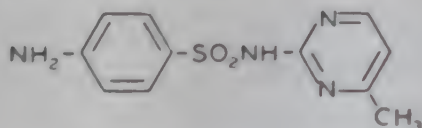
**Solution Sodium Sulfadiazine 5%:** 50 cc. ampuls. A solution containing 50 mg. of sodium sulfadiazine in each cubic centimeter.

U. S. patents 2,407,966 and 2,410,793.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Powder Sodium Sulfadiazine (Sterile):** 5 Gm. vials.

**SULFAMERAZINE-U.S.P.** —  $N^1$ -(4-Methyl-2-pyrimidyl)sulfanilamide.—“Sulfamerazine, dried at  $105^\circ$  for 4 hours, contains not less than 99 per cent of  $C_{11}H_{12}N_4O_2S$ .” *U.S.P.* The structural formula of sulfamerazine may be represented as follows:



**Physical Properties.**—Sulfamerazine occurs as white or faintly yellowish-white crystals or powder. It has a slightly bitter taste and is odorless or nearly so. It is stable in air but slowly darkens on exposure to light. One gram of sulfamerazine dissolves in about 6,250 cc. of water at  $20^\circ$  and in about 3,300 cc. at  $37^\circ$ . It is readily soluble in dilute mineral acids and in solutions of potassium, ammonium and sodium hydroxides. It is sparingly soluble in acetone, slightly soluble in alcohol, and very slightly soluble in ether and in chloroform.

**Actions and Uses.**—See the general statement on sulfonamides and on pyrimidine derivatives.

**Dosage.**—In the treatment of acute pneumococcic, streptococcic and meningococcic infections the maintenance of 10 to 15 mg. of sulfamerazine per 100 cc. of blood will usually be sufficient. Blood serum concentrations of this magnitude may be attained within 4 hours by the oral administration of 3 or 4 Gm. of sulfamerazine as an initial dose, followed by 1 Gm. every 8 hours. This schedule should be continued for 72 hours after the temperature, pulse and respiration rates return to normal.

For infants under 6 months of age, the initial dose is 0.5 Gm.

followed by 0.25 Gm. every 12 hours thereafter; infants 6 months to 3 years, 1 Gm. initial dose and 0.5 Gm. every 12 hours; children 3 to 10 years, 1.5 Gm. initial dose and 1 Gm. every 12 hours. In severe infections the dosage may be increased by 50 per cent.

**ABBOTT LABORATORIES**

**Dulcet Tablets Sulfamerazine: 0.3 Gm.**

U. S. trademark 500,527 (Dulcet).

**Tablets Sulfamerazine: 0.5 Gm.**

**AMERICAN PHARMACEUTICAL COMPANY, INC.**

**Tablets Sulfamerazine: 0.5 Gm.**

**BREWER & COMPANY, INC.**

**Tablets Sulfamerazine: 0.5 Gm.**

**LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY**

**Powder Sulfamerazine: 113 and 454 Gm. packages.**

**Tablets Sulfamerazine: 0.5 Gm.**

**ELI LILLY & COMPANY**

**Tablets Sulfamerazine: 0.5 Gm.**

**S. E. MASSENGILL COMPANY**

**Tablets Sulfamerazine: 0.5 Gm.**

**PARKE, DAVIS & COMPANY**

**Tablets Sulfamerazine: 0.5 Gm.**

**PHYSICIANS' DRUG & SUPPLY COMPANY**

**Tablets Sulfamerazine: 0.5 Gm.**

**SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.**

**Powder Sulfamerazine: 113 and 454 Gm. containers.**

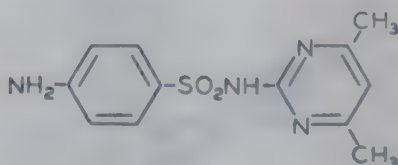
**Tablets Sulfamerazine: 0.5 Gm.**

U. S. patent 2,407,966.

**THE UPJOHN COMPANY**

**Tablets Sulfamerazine: 0.5 Gm.**

**SULFAMETHAZINE.** — N<sup>1</sup>-(4,6-Dimethyl-2-pyrimidyl)sulfanilamide.—The structural formula of sulfamethazine may be represented as follows:



**Physical Properties.**—Sulfamethazine is a white to yellow-white,

almost odorless powder with a slightly bitter taste, which may darken on exposure to light. It melts between 197 and 200°. It is freely soluble in dilute mineral acids and aqueous solutions of potassium hydroxide and sodium hydroxide, soluble in acetone, slightly soluble in alcohol and very slightly soluble in water.

**Actions and Uses.**—See the general statement on sulfonamides and on pyrimidine derivatives.

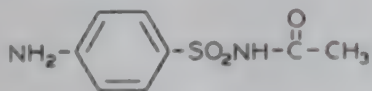
**Dosage.**—When administered by the oral route to patients suffering from severe infections, the initial dose should be based on 0.1 Gm. per kilogram of body weight but the maximum initial dose of sulfamethazine should not exceed 5 Gm. The maintenance dose of this drug in adults is 1 Gm. given at intervals of 6 hours. In children, one-fourth of the initial dose given at intervals of 6 hours constitutes an adequate maintenance dose.

### Sulfacetamide

Sulfacetamide is readily absorbed from the gastro-intestinal tract when it is given per os. Its distribution and degree of conjugation in the tissues are similar to those of sulfanilamide. The concentrations of sulfacetamide in the blood are proportional to the oral dose administered; the concentrations which pass into the spinal, pleural and peritoneal fluids are lower than those in the blood. Sulfacetamide is excreted primarily in the urine, in which both free and conjugated forms are found.

Sulfacetamide has a greater antibacterial activity against gram-positive cocci than against gram-negative bacilli, but it has a considerable effect against certain species of the latter group. Its range of use is similar to that of the pyrimidines. Clinically it may be employed in certain beta hemolytic streptococcic, pneumococcic, staphylococcic, gonococcic, meningococcic infections, and also in some diseases produced by *E. coli*, *A. aerogenes* and the Koch-Weeks bacillus. Sulfacetamide is not effective against systemic infections produced by *Ps. aeruginosa* or *B. proteus*. Its sodium derivative has been widely used for topical treatment of certain infections of the eye because of the rarity of sensitization reactions.

**SULFACETAMIDE.** — Sulamyd (SCHERING). — N-Sulfanilylaceta-  
mide.—N<sup>1</sup>-acetylsulfanilamide.—The structural formula of sulfa-  
cetamide may be represented as follows:



**Physical Properties.**—Sulfacetamide is an odorless, white, crystalline powder with a characteristic sour taste. It melts between 181 and 184° and decomposes with the evolution of gas between 190 and 195°. One part of sulfacetamide is soluble in about 140 parts of water. It is freely soluble in dilute mineral acids and aqueous solutions of potassium hydroxide and sodium hydroxide, soluble in alcohol, slightly soluble in ether, very slightly soluble in chloroform



and practically insoluble in benzene. Aqueous solutions are stable only in the pH range of 7 to 9 and are sensitive to light.

**Actions and Uses.**—See the general statement on sulfonamides and on sulfacetamide. Sulfacetamide possesses the advantage of greater solubility in the urine than the pyrimidine derivatives and therefore has less tendency to produce concretions in the urinary tract.

**Dosage.**—For adults, 1 Gm. of sulfacetamide is given three times daily after meals; for children, 0.06 Gm. per kilogram of body weight is given daily (approximately 0.5 Gm. per 15 lb.) in three equally divided doses after meals. The drug should be continued for at least a week after all symptoms have disappeared. If no improvement occurs after 10 days of treatment, the drug usually can be considered to have failed in its purpose. For prophylactic use, 0.5 Gm. three times daily after meals is recommended for 24 hours prior to and 48 hours after manipulative or surgical procedures on the genito-urinary tract.

Blood levels should be determined during administration of the drug. In cases of impaired kidney function with above average blood concentration and in any case when the blood level exceeds 12 mg. per cent of free sulfacetamide, the drug should be discontinued and fluids forced.

#### CHEMO PURO MANUFACTURING CORPORATION

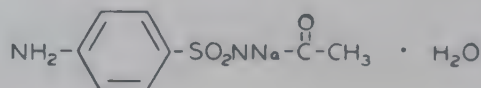
**Powder Sulfacetamide:** Bulk; for manufacturing use.

#### SCHERING CORPORATION

**Tablets Sulamyd:** 0.5 Gm.

U. S. patent 2,411,495. U. S. trademark 379,386.

**SODIUM SULFACETAMIDE.**—**Sodium Sulamyd (SCHERING).**—The monohydrated sodium salt of N-sulfanilylacetamide.—The structural formula may be represented as follows:



**Physical Properties.**—Sulfacetamide sodium is a white, odorless, bitter, crystalline powder. One part of sulfacetamide sodium is soluble in 2.5 parts of water. It is sparingly soluble in alcohol and practically insoluble in benzene, chloroform and ether. The pH of a 5 per cent solution is between 8.0 and 9.5. Aqueous solutions of sulfacetamide sodium must be refrigerated and protected from light.

**Actions and Uses.**—See the general statement on sulfonamides and on sulfacetamide.

The sodium salt is highly soluble at the physiologic pH of 7.4; therefore, it is especially suited, as a solution, for repeated topical application in the local management of ophthalmic infections susceptible to sulfonamide therapy. These include corneal ulcer, blepharitis, blepharoconjunctivitis, dacryocystitis, infections of the eye socket, trachoma and sties.

Local sensitivities frequently noted with other sulfonamides rarely are encountered with sodium sulfacetamide. Care should be exercised, however, to observe the first evidence of any sensitivity, and the drug should be abandoned on the appearance of any undesirable reaction. Do not use with silver preparations.

**Dosage.**—Sodium sulfacetamide is topically applied to the eye as a 30 per cent solution or as a 10 per cent ointment. The ointment should not be employed in the presence of penetrating wounds of the cornea and is ordinarily reserved for night time application as an adjunct to the use of the solution during the day. Prophylactic instillation of one drop of a 30 per cent solution four to six times daily is recommended to be continued for 2 days following the epithelization of lesions resulting from corneal abrasions, lacerations, burns or the removal of a foreign body. In acute infections, 1 or 2 drops every 2 hours, or less frequently, is used during the day according to severity; in chronic infections, 1 or 2 drops three or four times daily is considered adequate. At bedtime, application of a small amount of a 10 per cent ointment to the lower lid is recommended.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Sulfacetamide Sodium:** Bulk; for manufacturing use.

#### SCHERING CORPORATION

**Ophthalmic Ointment Sodium Sulamyd 10%:** 3.54 Gm. tubes. An ointment containing 0.1 Gm. of sodium sulfacetamide in each gram.

**Ophthalmic Solution Sodium Sulamyd 30%:** 15 cc. bottles. A solution containing 0.3 Gm. of sodium sulfacetamide in each cubic centimeter. Buffered with 0.2 per cent sodium dihydrogen phosphate. Preserved with 0.15 per cent sodium thiosulfate, 0.05 per cent methylparaben and 0.01 per cent propylparaben.

U. S. patent 2,411,495. U. S. trademark 379,386.

### *Sulfathiazole Derivatives*

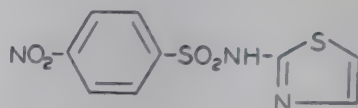
The actions and uses of phthalylsulfathiazole and succinylsulfathiazole resemble those of sulfaguanidine. Each has the property of suppressing the growth of bacteria in the large bowel and hence may be used preoperatively and postoperatively in surgical procedures on the colon. Each may be used as an adjunct to other methods of treatment in the control of acute and chronic ulcerative colitis.

These derivatives of sulfathiazole are relatively insoluble, and are poorly absorbed from the gastro-intestinal tract; they rarely reach blood concentrations exceeding 2 mg. per 100 cc. of blood. Toxic reactions to therapeutic doses therefore are rare. Since both are poorly absorbed, phthalylsulfathiazole and succinylsulfathiazole suppress bacteria in the large bowel by virtue of their high concentration in the lumen of that viscus.

*p*-Nitrosulfathiazole should be used only for rectal injection as

an adjunct in the local treatment of nonspecific ulcerative colitis and proctitis. It probably acts by altering the bacterial flora in the large bowel. It is of more value when the lesions are confined to the sigmoid than when they are diffused through the bowel. Little of the compound is absorbed from the bowel, hence only small amounts pass into the blood.

***p*-NITROSULFATHIAZOLE.**—Nisulfazole (BREON).—2-(*p*-Nitrophenylsulfonamido)thiazole.—The structural formula of *p*-nitrosulfathiazole may be represented as follows:



***Physical Properties.***—*p*-Nitrosulfathiazole is a pale yellow powder. It melts between 255 and 262°. It is slightly soluble in alcohol, very slightly soluble in chloroform, ether and water and practically insoluble in benzene. It is freely soluble in ammonia and sodium hydroxide T.S.

***Actions and Uses.***—See the general statement on sulfonamides and on sulfathiazole derivatives.

***Dosage.***—A 10 per cent stabilized suspension of *p*-nitrosulfathiazole undiluted, or diluted with equal parts of water, is injected rectally by means of a bulb syringe, preferably with the patient in the knee-chest position. The average initial dose is 10 cc. of the 10 per cent suspension, administered after each stool and at bedtime. Larger initial doses of 30 to 60 cc. given four times daily may be required. After improvement is observed, 15 to 30 cc. is usually given once daily at bedtime or less often as needed to maintain freedom from symptoms. Maintenance treatment is advised for 2 to 4 weeks after the mucosa appears normal.

Signs of toxicity from absorption of the drug, which may be due to the presence of large denuded areas of the mucous membrane of the bowel, usually subside promptly upon discontinuance of therapy. Blood or urine levels of the drug may be determined by using a modified application of the method of Bratton and Marshall. (See the general statement on sulfonamide compounds under *Toxicity*.)

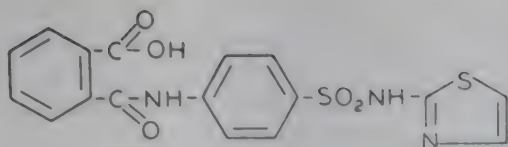
GEORGE A. BREON & COMPANY

**Suspension Nisulfazole 10%:** 296 cc. bottles. A suspension of 0.1 Gm. of *p*-nitrosulfathiazole in each cubic centimeter. Preserved with oil of peppermint and benzalkonium chloride.

U. S. trademark 418,348.

**PHTHALYLSULFATHIAZOLE-U.S.P.**—Sulfathalidine (STIARP & DOHME).—4'-(2-Thiazolylsulfamyl)phthalanilic acid.—“Phthalylsulfathiazole, dried at 105° for 4 hours, contains not less than 98 per cent of C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub>.” U.S.P. The structural formula of phthalylsulfathiazole may be represented as follows:





Phthalylsulfathiazole may be prepared by the condensation of sulfathiazole with phthalic anhydride.

**Physical Properties.**—Phthalylsulfathiazole occurs as a white or faintly yellowish-white, crystalline powder. It has a slightly bitter taste and is odorless. It may darken slowly on long exposure to light. Phthalylsulfathiazole is practically insoluble in water and in chloroform. It is slightly soluble in alcohol and very slightly soluble in ether. It is readily soluble in solutions of alkali hydroxides and their carbonates and in hydrochloric acid.

**Actions and Uses.**—See the general statement on sulfonamides and on sulfathiazole derivatives.

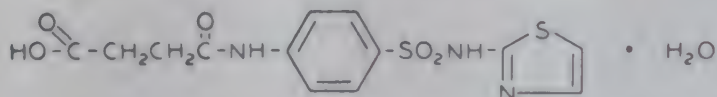
**Dosage.**—Orally, in tablet form, 0.05 to 0.1 Gm. per kilogram of body weight daily is given in equally divided doses at intervals of 4, 6 or 8 hours, depending on the total dose to be administered. The average daily adult dose is provided by eight to twelve 0.5 Gm. tablets and should not exceed 8 Gm. Smaller doses, as indicated by response, may be continued for up to 8 weeks or even longer for the management of ulcerative colitis. As a preliminary adjunct to intestinal surgery, an initial dose of 0.125 Gm. per kilogram is given, followed by the same amount daily in divided doses given at equal intervals, comprising three, four or six doses per day, for 3 to 5 days prior to operation.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Tablets Sulfathalidine: 0.5 Gm.**

U. S. patents 2,324,013, 2,324,015 and 2,576,825. U. S. trademark 408,341.

**SUCCINYLSULFATHIAZOLE-U.S.P.** — Sulfasuxidine (SHARP & DOHME). — *p*-(2-Thiazolylsulfamyl)succinanilic acid. — "Succinylsulfathiazole, dried at 105° for 4 hours, contains not less than 99 per cent of  $C_{13}H_{13}N_3O_5S_2$ ." *U.S.P.* The structural formula of succinylsulfathiazole may be represented as follows:



**Physical Properties.**—Succinylsulfathiazole occurs as a white or yellowish-white, crystalline powder. It is odorless and is stable in air but slowly darkens on exposure to light. One gram dissolves in about 4,800 cc. of water with the evolution of carbon dioxide. It is sparingly soluble in alcohol and in acetone and is insoluble in chloroform and in ether.

**Actions and Uses.**—See the general statement on sulfonamides and on sulfathiazole derivatives.

**Dosage.**—The initial preoperative dose is 0.25 Gm. per kilogram of body weight by mouth, followed by a maintenance dose of 0.25 Gm. per kilogram daily in six equal portions at 4-hour intervals. The postoperative dose is 0.25 Gm. per kilogram daily for 1 or 2 weeks, depending on the postoperative condition. Postoperative administration should be begun as soon as the patient can take an ounce of water without undue nausea.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

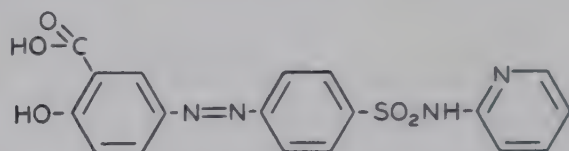
**Powder Sulfasuxidine:** 113 and 454 Gm. glass jars.

**Tablets Sulfasuxidine:** 0.5 Gm.

U. S. patents 2,324,013, 2,324,014 and 2,576,825. U. S. trademark 394,111.

### Other Sulfonamide Compounds

**SALICYLAZOSULFAPYRIDINE.**—Azulfidine (PHARMACIA).—5-[*p*-(2-Pyridylsulfamyl)phenylazo]salicylic acid.—The structural formula of salicylazosulfapyridine may be represented as follows:



**Physical Properties.**—Salicylazosulfapyridine is a brownish yellow, odorless powder, which melts between 220 and 240° (with decomposition). It is slightly soluble in alcohol and practically insoluble in benzene, chloroform, ether and water.

**Actions and Uses.**—Salicylazosulfapyridine shares the actions of related sulfonamide compounds, including the potential toxic effects of sulfapyridine. Because the drug has been found to have a special affinity for connective tissue, it is proposed for use in chronic ulcerative colitis. Available clinical evidence confirms its usefulness only for this purpose and does not justify conclusions that its selective retention in connective tissue is of therapeutic significance or that it is clinically superior to other sulfonamide compounds in the management of this condition.

Salicylazosulfapyridine is broken down in the body to amino-salicylic acid and sulfapyridine. The drug is excreted through the kidneys and is colorimetrically detectable in the urine. It produces an orange-yellow color when the urine is alkaline and no color when the urine is acid.

**Dosage.**—Salicylazosulfapyridine is administered orally only. The average dose for adults is 1 Gm. four to six times daily with no interval of more than 8 hours between doses. Larger doses may be employed in severe cases. For children over 7 years of age, the average dose is 0.5 to 1 Gm. three to six times daily; children 5 to 7 years of age, 0.25 to 0.5 Gm. three to six times daily.

Usual doses produce a blood concentration of sulfapyridine which

seldom exceeds 1 to 2 mg. per 100 cc., a level considerably lower than that produced with the formerly recognized use of sulfa-pyridine as such. If slight nausea occurs, the dosage should be reduced by one-half. If nausea is severe, treatment should be discontinued for 2 days and then resumed at one-half the original dosage for 3 days before returning to full dosage. Results of therapy should be followed by rectoscopy. Treatment should be continued until such observations reveal satisfactory response even when diarrhea has stopped. Following initial rectoscopic response, adult dosage should be reduced to 0.5 Gm. three times daily.

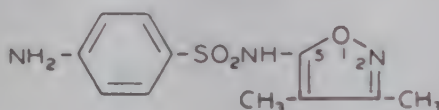
Because of the unusual toxicity of sulfapyridine as compared with other sulfonamides, patients should be especially observed for toxic manifestations characteristic of this group of drugs. If leukopenia or severe drug fever and exanthema appear, therapy should be immediately discontinued. Periodic blood counts and careful observation are essential.

#### PHARMACIA LABORATORIES, INC.

Tablets Azulfidine: 0.5 Gm.

U. S. patent 2,396,145. U. S. trademark 571,960.

**SULFISOXAZOLE.**—*Gantrisin* (HOFFMANN-LAROCHE).—N<sup>1</sup>-3,4-Dimethyl-5-isoxazolylsulfanilamide.—The structural formula of sulfisoxazole may be represented as follows:



**Physical Properties.**—Sulfisoxazole is a white, odorless, slightly bitter, crystalline powder. It melts between 192 and 195°. It is freely soluble in diluted hydrochloric acid and soluble in alcohol.

**Actions and Uses.**—Sulfisoxazole shares the actions and uses of other sulfonamide derivatives. (See the general statement on sulfonamides.) There is some evidence to indicate that sulfisoxazole is an antibacterial agent of choice against proteus infections. It may vary in its effectiveness against different strains of sulfonamide-sensitive micro-organisms. Because of its relatively high solubility in body fluids, the drug is less likely to produce crystalluria and renal blocking than less soluble sulfonamide derivatives employed singly; otherwise it has the same potentiality for toxic reactions.

**Dosage.**—The initial oral dose for adults is 4 to 6 Gm., followed by 1 to 2 Gm. every 4 hours until temperature has been normal for at least 48 hours.

For children, 50 to 100 mg. per kilogram of body weight may be given orally initially, followed by 200 mg. per kilogram of body weight daily in divided doses at 4-hour intervals, until temperature has been normal for at least 48 hours.

#### HOFFMANN-LAROCHE, INC.

Powder *Gantrisin*: 4.72, 113.4 and 454 Gm. bottles.

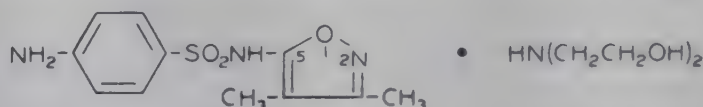


**Suspension Gantrisin Pediatric:** 118.3 and 473 cc. bottles. A suspension containing 0.1 Gm. of sulfisoxazole in each cubic centimeter. Preserved with 0.08 per cent methylparaben and 0.02 per cent propylparaben.

**Syrup Gantrisin:** 118.3 and 473 cc. bottles. A flavored syrup containing 0.1 Gm. of sulfisoxazole in each cubic centimeter.

**Tablets Gantrisin:** 0.5 Gm.

**SULFISOXAZOLE DIETHANOLAMINE.**—**Gantrisin Diethanolamine** (HOFFMANN-LA ROCHE).—2,2'-Iminodiethanol salt of N<sup>1</sup>-3,4-dimethyl-5-isoxazolylsulfanilamide.—Sulfisoxazole diethanolamine is made by adding enough diethanolamine to a solution of sulfisoxazole to bring the pH to about 7.5. The structural formula of sulfisoxazole diethanolamine may be represented as follows:



**Actions and Uses.**—Sulfisoxazole diethanolamine is used as a salt of sulfisoxazole to make the drug more soluble at the physiologic pH range of 6.0 to 7.5. Diethanolamine reacts with the sulfisoxazole to form a soluble salt. The diethanolamine salt, therefore, is used in solution for systemic administration of the drug by slow intravenous, intramuscular or subcutaneous injection when sufficient blood levels cannot be maintained by oral administration alone, and for instillation of drops or ointment in the eye for the local treatment of susceptible infections. The salt shares the action of its parent, sulfisoxazole, which is employed for oral administration. (See the monograph on sulfisoxazole and the general statement on sulfonamides.)

**Dosage.**—A solution of 40 per cent sulfisoxazole in the form of the diethanolamine salt may be used for slow intravenous or intramuscular injection. No more than 5 cc. intramuscularly should be injected at any one site. For subcutaneous administration, the sulfisoxazole diethanolamine solution containing 40 per cent sulfisoxazole must be diluted with sterile distilled water to 5 per cent or less. The dosage should not exceed that for oral administration of the parent drug, sulfisoxazole (see the monograph on sulfisoxazole). Intravenous, intramuscular or subcutaneous injection should not replace oral administration except when the drug cannot be administered adequately by that route.

For ophthalmic use, a solution or ointment of 4 per cent sulfisoxazole in the form of the diethanolamine salt may be used for topical application in the conjunctival sac. The solution is approximately isotonic. Two or three drops of solution or a small amount of ointment may be instilled into the eye three or more times daily. Occasionally, a transient, slight burning or stinging sensation may occur immediately following instillation, but this usually disappears in a few minutes.

Ophthalmic preparations of sulfisoxazole diethanolamine should be used cautiously, especially in patients who have previously exhibited sensitivity to sulfonamides. If undesirable reactions occur during such use, the drug should be discontinued immediately. Silver preparations must not be used concurrently for ophthalmic application.

#### HOFFMANN-LAROCHE, INC.

**Ophthalmic Ointment Gantrisin Diethanolamine 4%:** 3.54 Gm. tubes. An ointment containing 40 mg. of sulfisoxazole in the form of the diethanolamine salt in each gram. Preserved with 0.002 per cent phenylmercuric nitrate.

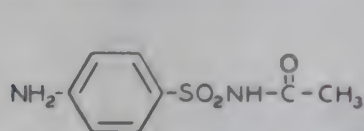
**Ophthalmic Solution Gantrisin Diethanolamine:** 30 cc. dropper bottles. A solution containing 40 mg. of sulfisoxazole as the diethanolamine salt.

**Solution Gantrisin Diethanolamine:** 5 and 10 cc. ampuls. A solution containing 0.4 Gm. of sulfisoxazole as the diethanolamine salt in each cubic centimeter.

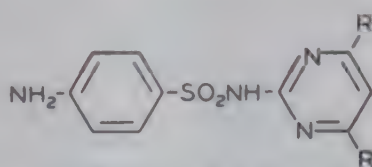
### Sulfonamide Mixtures

Mixtures of the three pyrimidine derivatives and of one or more of them with another sulfonamide have essentially the same actions and uses as the individual sulfonamides. These mixtures of sulfonamides were developed with the hope that efficacy would be retained while the tendency for crystals to form in the urine would be lessened and the toxicity to renal tubules decreased. Danger of damage to the kidneys during the use of these agents is diminished because each sulfonamide is present in less concentration than when used alone and renal excretion of the sulfonamides apparently is individual rather than additive. The therapeutic efficacy of the mixtures, however, is that of the sum of the components.

**ACET-DIA-MER-SULFONAMIDES.**—Cetazine (BOWMAN BROS.).—Dorsulfas (SMITH-DORSEY).—Incorposul (BLUE LINE).—Tricombisul (SCHERING).—A sulfonamide mixture containing equal weights of sulfacetamide, sulfadiazine-U.S.P. and sulfamerazine-U.S.P., to which a suitable compatible agent may be added to increase the pH of the urine. The structural formulas of the sulfonamides may be represented as follows.



Sulfacetamide



Sulfadiazine,  $R = R' = H$   
Sulfamerazine,  $R = H, R' = CH_3$

**Actions and Uses.**—See the general statement on sulfonamide

mixtures. For specific indications and contraindications to the use of the drugs, see the general statement on sulfonamides.

**Dosage.**—The mixture of acet-dia-mer-sulfonamides is administered orally. In adults, 4 Gm. total sulfonamides is given as the initial dose, followed by 1 Gm. every 4 hours until signs of infection have been absent for at least 48 hours. Then 3 to 4 Gm. in divided doses is given daily for an additional 2 to 3 days depending upon the type and severity of infection. In children, the average daily dose should be calculated on the basis of 0.1 Gm. per kilogram of body weight; one-third of this amount is given as the initial dose, followed by one-sixth of the total daily dose every 4 hours. This amount should be continued as a maintenance dose until signs of infection have subsided for at least 36 hours. Thereafter, two-thirds to one-half of the original maintenance dose may be given for an additional 2 to 3 days, again depending upon the type and severity of the infection. The blood concentration of sulfonamides should be maintained between 5 and 15 mg. per 100 cc.

#### THE BLUE LINE CHEMICAL COMPANY

**Suspension Incorposul:** 60 and 473 cc. bottles. A suspension containing 44 mg. each of sulfacetamide, sulfadiazine and sulfamerazine in each cubic centimeter. Preserved with 0.05 per cent methylparaben and 0.01 per cent propylparaben.

**Tablets Incorposul:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfacetamide, sulfadiazine and sulfamerazine.

#### THE BOWMAN BROS. DRUG COMPANY

**Hexad Tablets Cetazine:** 0.25 Gm. Each tablet contains 83 mg. each of sulfacetamide, sulfadiazine and sulfamerazine.

#### SCHERING CORPORATION

**Liquid Tricombisul:** 473 cc. bottles. A suspension containing 42 mg. each of sulfacetamide, sulfadiazine and sulfamerazine in each cubic centimeter. Preserved with 0.05 per cent methylparaben and 0.01 per cent propylparaben.

**Tablets Tricombisul:** 0.5 Gm. Each tablet contains 0.166 Gm. each of sulfacetamide, sulfadiazine and sulfamerazine.

U. S. trademark 538,898.

#### SMITH-DORSEY, DIVISION OF THE WANDER COMPANY

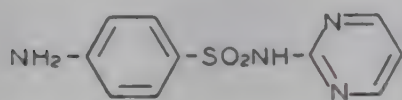
**Suspension Dorsulfas:** 473 cc. bottles. A suspension containing 33 mg. each of sulfacetamide, sulfadiazine and sulfamerazine in each cubic centimeter.

**Tablets Dorsulfas:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfacetamide, sulfadiazine and sulfamerazine.

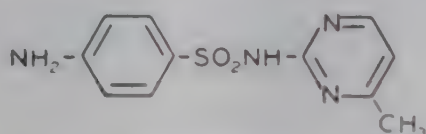
**DIA-MER-SULFONAMIDES.** — Bi-Sulfazine (WARREN-TEED). — Bisulfon (VELTEX). — Diamerzine (VALE). — Disulfyn (RORER). — Duo-Sulfanyl (FUNK). — Duozone (ABBOTT). — Mer-Diazine (MCNEIL). —



**Sul-Di-Mill (MILLER).**—**Sulfadimer (PITMAN-MOORE).**—**Sulfonamides Duplex (LILLY).**—**Sulmeradine (PHYSICIANS' DRUG).**—A mixture of equal weights of sulfadiazine and sulfamerazine to which there may or may not be added a suitable compatible agent to increase the pH of the urine. The structural formulas of the sulfonamides may be represented as follows:



Sulfadiazine



Sulfamerazine

**Actions and Uses.**—See the general statement on sulfonamides and on sulfonamide mixtures.

**Dosage.**—In the treatment of acute pneumococcic, streptococcic and meningococcic infections the maintenance of a blood concentration of 10 to 15 mg. of total sulfonamides per 100 cc. is usually sufficient. Blood serum concentrations of this magnitude may be attained within 4 hours by the oral administration of 3 or 4 Gm. of total sulfonamides as an initial dose, followed by 1 Gm. every 6 hours. This dosage should be continued for 72 hours after the temperature and pulse and respiration rates return to normal. In severe infections it may be desirable to increase the dosage; however, concentrations in excess of 12 mg. of the combined drugs per 100 cc. of blood are rarely needed.

For children the initial dose of 65 to 100 mg. total sulfonamides per kilogram of body weight is followed by one-quarter the initial dose every 6 hours. Dosage should be adjusted to meet the requirements of each case.

#### ABBOTT LABORATORIES

**Dulcet Tablets Duozone:** 0.3 Gm. Each tablet contains 0.15 Gm. each of sulfadiazine and sulfamerazine.

0.15 Gm. Each tablet contains 75 mg. each of sulfadiazine and sulfamerazine.

U. S. trademark 500,527 (Dulcet).

**Suspension Duozone with Sodium Citrate:** 473 cc. and 3.78 liter bottles. A suspension containing 30 mg. each of sulfadiazine and sulfamerazine and 0.3 Gm. of sodium citrate in each cubic centimeter.

**Tablets Duozone:** 0.5 Gm. Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

U. S. trademark 546,525.

#### CASIMIR FUNK LABORATORIES

**Syrup Duo-Sulfanyl with Sodium Citrate:** 118.3 cc., 473 cc. and 3.78 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine and 0.1 Gm. of sodium citrate in each cubic centimeter.

**ELI LILLY & COMPANY**

**Savorets (*Flavored Tablets*) Sulfonamides Duplex:** Each tablet contains 0.125 Gm. each of sulfadiazine and sulfamerazine.

**Suspension Sulfonamides Duplex:** 473 cc. bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine in each cubic centimeter.

**Tablets Sulfonamides Duplex:** Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

**MCNEIL LABORATORIES, INC.**

**Liquoid Mer-Diazine:** 120 and 480 cc. bottles. A suspension containing 50 mg. each of sulfamerazine and sulfadiazine in each cubic centimeter.

**E. S. MILLER LABORATORIES, INC.**

**Tablets Sul-Di-Mill with Sodium Bicarbonate:** Each tablet contains 0.22 Gm. each of sulfadiazine and sulfamerazine and 0.3 Gm. sodium bicarbonate.

**PHYSICIANS' DRUG & SUPPLY COMPANY**

**Tablets Sulmeradine:** 0.5 Gm. Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

**PITMAN-MOORE COMPANY**

**Magmoid Sulfadimer with Sodium Lactate:** 354.9 cc. and 3.78 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine and 0.1 Gm. of sodium lactate in each cubic centimeter.

**WILLIAM R. RORER, INC.**

**Suspension Disulfyn:** 60 and 473 cc. bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine in each cubic centimeter.

**Tablets Disulfyn:** Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

**THE VALE CHEMICAL COMPANY, INC.**

**Tablets Diamerzine:** 0.5 Gm. Each tablet contains 0.25 Gm. each of sulfadiazine and sulfamerazine.

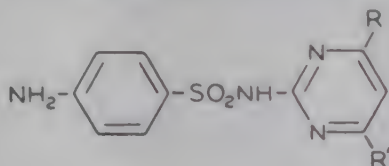
**VELTEX COMPANY**

**Suspension Bisulfon with Sodium Lactate:** 480 cc. and 3.84 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine and 0.1 Gm. sodium lactate in each cubic centimeter.

**THE WARREN-TEED PRODUCTS COMPANY**

**Suspension Bi-Sulfazine:** 473 cc. and 3.78 liter bottles. A suspension containing 50 mg. each of sulfadiazine and sulfamerazine in each cubic centimeter.

**METH-DIA-MER-SULFONAMIDES.**—Metha-Mer diazine (MCNEIL).—Multazine (KREMERS-URBAN).—Ray-Tri-Mides (RAYMER).—Sulfaloid (LLOYD & DABNEY).—Sulfa-tri-azine (THOMPSON).—Sulfatryl (WAMPOLE).—Terfonyl (SQUITB).—Tersulfas (BOYLE).—Trifonamide (VANPELT & BROWN).—Trionamide (FLINT, EATON).—Tripazine (EATON).—Tri-Sulfameth (FUNK).—Trisulfazine (CENTRAL).—Truozine (ABBOTT).—A sulfonamide mixture containing equal weights of sulfadiazine-U.S.P., sulfamerazine-U.S.P. and sulfamethazine, to which there may or may not be added a suitable compatible agent to increase the pH of the urine. The structural formula of the sulfonamides may be represented as follows:



SULFADIAZINE,  $R = R' = H$

SULFAMERAZINE,  $R = H, R' = CH_3$

SULFAMETHAZINE,  $R = R' = CH_3$

**Actions and Uses.**—See the general statement on sulfonamides and on sulfonamide mixtures.

**Dosage.**—In the treatment of acute pneumococcic, streptococcic and meningococcic infections the maintenance of a blood concentration of total sulfonamide drugs of 10 to 15 mg. per 100 cc. will usually be sufficient. Blood serum concentrations of this magnitude may be attained within 4 hours by the oral administration of 3 or 4 Gm. of the triple sulfonamide mixture as an initial dose, followed by 1 Gm. every 6 hours. This dosage should be continued for 72 hours after the temperature and pulse and respiration rates return to normal. In severe infections, it may be desirable to increase the dosage. However, blood concentrations of the combined drugs in excess of 12 mg. per 100 cc. are rarely needed.

For children an initial dose of 65 to 100 mg. of total sulfonamide drugs per kilogram of body weight is followed by one-quarter the initial dose every 6 hours. Dosage should be adjusted to meet the requirements of the particular case.

Sulfonamide mixtures are suited only for oral administration.

#### ABBOTT LABORATORIES

**Suspension Truozine with Sodium Citrate (Flavored):** 473 cc. bottles. A suspension containing 20 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.3 Gm. of sodium citrate in each cubic centimeter.

**Dulcet Tablets Truozine:** Each tablet contains 0.1 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 500,527 (Dulcet).

**Tablets Truozine:** Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 565,944.



**BOYLE & COMPANY**

**Tablets Tersulfas:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

**THE CENTRAL PHARMACAL COMPANY**

**Palatabs Trisulfazine:** 0.25 Gm. Each tablet contains 83 mg. each of sulfadiazine, sulfamerazine and sulfamethazine.

**Suspension Trisulfazine with Sodium Lactate:** 60 cc., 473 cc. and 3.78 liter bottles. A stable suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.1 Gm. of sodium lactate in each cubic centimeter. Preserved with methylparaben and propylparaben.

**Tablets Trisulfazine:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

**EATON LABORATORIES, INC.**

**Tablets Tripazine:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

**FLINT, EATON & COMPANY**

**Suspension Trionamide with Sodium Citrate:** 60 cc., 473 cc. and 3.78 liter bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 66 mg. of sodium citrate in each cubic centimeter.

**CASIMIR FUNK LABORATORIES, INC.**

**Syrup Tri-Sulfameth:** 118.3 cc., 473 cc. and 3.78 liter bottles. A syrup containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.1 Gm. of sodium citrate in each cubic centimeter.

**Tablets Tri-Sulfameth:** 0.5 Gm. Each tablet contains 0.165 Gm each of sulfadiazine, sulfamerazine and sulfamethazine.

**KREMERS-URBAN COMPANY**

**Tablets Multazine:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

**LLOYD & DABNEY COMPANY, INC.**

**Tablets Sulfaloid:** 0.25 Gm. Each tablet contains 83 mg. each of sulfadiazine, sulfamerazine and sulfamethazine.

0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

**MCNEIL LABORATORIES, INC.**

**Liquoid Metha-Merdiazine:** 120 cc. and 480 cc. bottles. A homogenized dispersion containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

**Tablets Metha-Mer diazine:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 533,769.

**PREMO PHARMACEUTICAL LABORATORIES, INC.**

**Suspension Meth-Dia-Mer-Sulfonamides:** 473 cc. bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

**Tablets Meth-Dia-Mer-Sulfonamides:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

**RAYMER PHARMACAL COMPANY**

**Suspension Ray-Tri-Mides:** 473 cc. and 3.78 liter bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

**E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION**

**Suspension Terfonyl:** 473 cc. bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter. Preserved with 0.05 per cent each of methylparaben and propylparaben.

**Tablets Terfonyl:** 0.5 Gm. Each tablet contains 0.167 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

U. S. trademark 536,646.

**MARVIN R. THOMPSON, INC.**

**Suspension Sulfa-tri-azine with Sodium Lactate:** 473 cc. and 3.78 liter bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.3 Gm. of sodium lactate in each cubic centimeter.

U. S. patent 2,460,437.

**VANPELT & BROWN, INC.**

**Suspension Trifonamide:** 360 cc. bottles. A suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine in each cubic centimeter.

**Tablets Trifonamide:** 0.5 Gm. Each tablet contains 0.166 Gm. each of sulfadiazine, sulfamerazine and sulfamethazine.

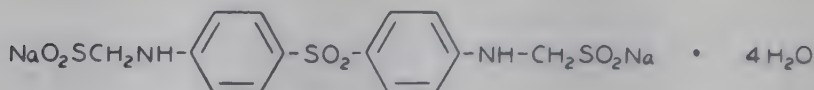
U. S. trademark 508,633.

**HENRY K. WAMPOLE & COMPANY, INC.**

**Granules Sulfatryl for Suspension with Sodium Citrate:** Flavored granules which when mixed with 60 cc. of water yield a suspension containing 33 mg. each of sulfadiazine, sulfamerazine and sulfamethazine and 0.1 Gm. of sodium citrate in each cubic centimeter.

## Sulfone Compounds

**SULFOXONE SODIUM.**—**Diasone Sodium (ABBOTT).**—Sulfoxone sodium consists chiefly of the active component, disodium [sulfonylbis(*p*-phenyleneimino)]dimethanesulfinate tetrahydrate.—Sulfoxone sodium contains not less than 77 per cent anhydrous disodium [sulfonylbis(*p*-phenyleneimino)]dimethanesulfinate. In the course of manufacture, sulfoxone sodium is commonly stabilized by the addition of about 10 per cent of sodium bicarbonate or disodium phosphate. The structural formula for the active component of sulfoxone sodium may be represented as follows:



**Physical Properties.**—Sulfoxone sodium is a pale yellow powder with a characteristic odor. It is very soluble in water and very slightly soluble in alcohol. The aqueous solution is clear and pale yellow.

**Actions and Uses.**—Sulfoxone sodium is indicated in the treatment of leprosy. Lesions usually do not progress under therapy, although not all respond favorably. The earliest and most frequent signs of response are healing of mucous membrane lesions followed by improvement in skin lesions. The latter consists of fading of macules and plaques, softening and flattening of nodules and decrease in diffuse infiltration. Nodules diminish in size and in most instances resorption is complete. Sometimes there is necrosis of nodules followed by ulceration and rapid healing.

The commonest toxic effect of the drug is a transient normocytic anemia but withdrawal is not indicated unless the anemia becomes severe. Usually, recovery from the anemia takes place between the third and sixth week of therapy. Methemoglobinemia, which occurs in about half the patients, is not an indication for withdrawal of the drug unless anoxemia is acute.

Other toxic effects are nausea, hematuria, drug rashes and leukopenia.

**Dosage.**—Treatment is started with small doses. The usual initial dose for adults is 0.3 Gm. daily. If no symptoms of intolerance appear during the first week of treatment, the dose may be increased to 0.6 Gm. daily. This dosage is continued for 2 or 3 weeks. If no symptoms of intolerance develop, the dose may be increased to 0.9 Gm. daily and continued at this rate for 6 months or more if no severe side effects develop. At least 6 months are required to evaluate therapeutic effect. Rest periods of 2 weeks every 2 months are advisable.

For children 6 to 12 years old the initial dose is 0.15 Gm. daily, increasing at monthly intervals to 0.6 Gm. if there are no contraindications. For children 4 to 6 years old the maximum



daily dose may be 0.45 Gm. Information concerning treatment of younger children is not available.

#### ABBOTT LABORATORIES

**Enterab Tablets Diasone Sodium: 0.33 Gm.**

U. S. patent 2,256,575 and Licensed under U. S. patent 2,234,981. U. S. trademarks 407,420 and 353,674 (Enterab).

## ANTIBIOTICS

The group of substances referred to as antibiotics are chemically dissimilar and, originally, were produced in cultures during the active growth phase of certain bacteria or molds. They have one property in common: they produce bacteriostatic or bactericidal effects against susceptible micro-organisms if conditions are propitious. The chemical formulas of penicillin, streptomycin, chloramphenicol, aureomycin and oxytetracycline have been wholly or partially described. Penicillin and chloramphenicol have been synthesized by chemical methods, and the latter is now produced commercially by a synthetic process. The pharmacologic properties of the various antibiotics must be considered separately because of the diversity among these substances.

**Bacterial Resistance.**—The selection of the proper and most effective antibiotic for the systemic treatment of particular infections is becoming more difficult as potent antibiotics with similar therapeutic powers appear. However, one important factor is the increasing resistance of some species of pathogenic micro-organisms to the antibacterial effects of certain antibiotics.

Reports from Australia, Great Britain and a number of places in the United States state that penicillin-resistant strains of *Staph. aureus* are being encountered frequently. A study of this phenomenon has shown that these strains of staphylococci are resistant because they produce penicillinase, the biologic antagonist of penicillin. According to some authorities, more than 50 per cent of the pathogenic strains of *Staph. aureus* isolated today are resistant to penicillin. This situation appears to exist also in relation to *Streptococcus fecalis* and certain of the nonhemolytic streptococci. However, there are no clinical reports that strains of pathogenic beta hemolytic streptococci (Lancefield's Group A), pneumococci, meningococci or gonococci have developed increased resistance to the antibacterial effects of penicillin.

With streptomycin and dihydrostreptomycin, the situation is even worse. One competent investigator has reported that, of the pathogenic strains of the following organisms which were isolated from diseased tissue in 1949, 33 per cent of the strains of *E. coli*, 45 per cent of the strains of *A. aerogenes*, 70 per cent of the strains of proteus, 77 per cent of the strains of *A. aeruginosa*, 33 per cent of the strains of nonhemolytic streptococci and 77 per cent of the strains of *Str. fecalis* were resistant, and often highly resistant, to the antibacterial effects of streptomycin. Another serious discovery has been made: Infants exposed to persons with infectious strepto-

mycin-resistant tuberculosis, have developed tuberculous meningitis primarily resistant to streptomycin. Resistance to streptomycin develops easily by mutation, or the selection out of resistant strains, of the micro-organism and, in the majority of instances of nontuberculous infections, develops within the first week of therapy.

**Indications.**—Penicillin G is still the antibiotic of choice for the systemic treatment of infections produced by beta hemolytic streptococci (Lancefield's Group A), pneumococci, meningococci, gonococci, the spirochetes, *Cl. welchii* and actinomycosis. Aureomycin and oxytetracycline are also effective in these infections, except that oxytetracycline is not effective in actinomycosis. In infections produced by *Staph. aureus*, *Str. fecalis*, *L. monocytogenes*, the Bacteroides and *Lept. icterohemorrhagica*, aureomycin and oxytetracycline are the most effective antibiotics. In tuberculosis, streptomycin and *p*-aminosalicylic acid should be used.

Aureomycin, chloramphenicol and oxytetracycline are equally effective in brucellosis, tularemia, bacillary infections caused by *E. coli*, *A. aerogenes*, *Kl. pneumoniae*, the *Shigella* group of infections, chancroid, granuloma inguinale, bacillary dysentery and rickettsial diseases.

Clinical reports seem to indicate that aureomycin, chloramphenicol and oxytetracycline are beneficial therapeutic agents in the treatment of whooping cough.

All are effective, but aureomycin particularly so, in psittacosis, lymphogranuloma venereum and primary atypical pneumonia. While all three are effective in certain stages of syphilis, their value, relative to penicillin, awaits further study.

Only chloramphenicol is really effective in typhoid fever. Chloramphenicol and aureomycin, used with a pyrimidine derivative of sulfanilamide, are of value in meningitis caused by *Hemophilus influenzae*. Aureomycin and oxytetracycline are effective in acute amebic dysentery. Aureomycin is the antibiotic of choice for local treatment of vaginitis produced by *Trichomonas vaginalis*.

Aureomycin, chloramphenicol and oxytetracycline may be used for the suppression of bacterial growth in the stool as a preoperative and postoperative prophylactic measure in surgery of the large bowel. Aureomycin has proved very effective as a prophylactic in puerperal sepsis. Penicillin is valuable in the prophylaxis of gonorrhea, syphilis, acute rheumatic fever and sepsis following the extraction of teeth or after "clean" surgery. Streptomycin is effective in the therapy of tissue infections produced by (nonresistant strains of) *Proteus* or *Pseudomonas aeruginosa* organisms. However, in infections caused by *Ps. aeruginosa*, polymyxin B is the antibiotic of choice. None of the antibiotics is of proved value in paratyphoid fevers and other salmonella infections. There is little or no evidence that any of the antibiotics is effective in the treatment of the common cold, influenza, measles, mumps, acute viral hepatitis, acute infectious mononucleosis, lymphocytic choriomeningitis, chicken pox, small pox, viral encephalitis and a number of other viral infections. Neither fungal diseases nor most parasitic infections respond to antibiotics.



**Toxicity.**—All currently accepted antibiotics produce toxic reactions in some people. Allergic reactions, manifested by various types of skin eruptions or lesions, with or without painful swollen joints, are common when penicillin, streptomycin or dihydrostreptomycin is administered to a sensitive patient. Persons allergic to procaine react similarly to procaine penicillin. Similar types of skin reactions have been rare during therapy with aureomycin, chloramphenicol or oxytetracycline. Contact dermatitis may be produced by antibiotics, particularly streptomycin and penicillin. Asthma has developed as a toxic reaction to penicillin by inhalation and lesions of the mucous membranes have followed penicillin (by mouth), aureomycin, chloramphenicol and oxytetracycline. Anaphylactic shock, with death, has occurred as a result of injection of penicillin or streptomycin. Drug fever is a common reaction to penicillin or streptomycin, but is rare when aureomycin, chloramphenicol or oxytetracycline is used. Renal injury from the use of these antibiotics has not been reported. Changes in the peripheral blood or the blood-forming organs have been reported only during the use of chloramphenicol. Mild hemolytic anemias, granulocytopenia, agranulocytosis and severe and fatal cases of aplastic anemia have been reported as toxic reactions produced by chloramphenicol. When this antibiotic is used its effect on the blood-forming organs must be carefully studied. Peripheral neuritis has been attributed to penicillin therapy. Vertigo, tinnitus, disturbances in equilibrium and deafness, due to eighth nerve injury, are well known as complications in therapy with streptomycin or dihydrostreptomycin. Although partial recovery of eighth nerve function may occur, numerous examples of permanent vestibular dysfunction and deafness have been reported, especially following the use of dihydrostreptomycin. Nausea and vomiting may be produced by aureomycin, chloramphenicol or oxytetracycline, the incidence increasing with the dose. There are at present no statistically sound data available as to the greatest offender among these three antibiotics, but it appears that the more highly integrated the patient, the greater is the probability that nausea and vomiting will develop. Loose stools or frank diarrhea may also result from the use of these agents. Granulocytopenia and fatal cases of aplastic anemia have been observed as toxic reactions in the course of therapy with chloramphenicol. Blood studies should be done frequently for all patients receiving this drug.

Because aureomycin, chloramphenicol and oxytetracycline have powerful suppressive effects on the normal bacterial flora of the mouth, vagina and large intestine, and abnormal flora elsewhere, superimposed infections (or infestations) with yeastlike organisms may occur. Hence, thrush and moniliasis of the skin, especially in the peri-anal region, and of the mucous surfaces of the vagina and lower rectum are not uncommon. Moniliasis of the lungs has followed the prolonged use of aureomycin, chloramphenicol or oxytetracycline for the treatment of bronchiectasis. All lesions of the skin or mucous membranes which occur in the course of therapy with aureomycin, chloramphenicol or oxytetracycline should be suspected as symptoms of moniliasis. Infections pro-



duced by monilia may also occur during penicillin therapy. It is possible also that these three antibiotics may, by altering the bacterial metabolism in the stool, produce mild states of vitamin deficiency, especially in relation to the vitamin B complex. This possibility must be considered when lesions of mucous membranes occur.

For tyrothricin see the chapter on local anti-infectives.

### Aureomycin

Thus far there are only biologic tests for measuring the absorption, distribution and excretion in body fluids and tissues of aureomycin. These give relative values only because aureomycin deteriorates in solution, making it difficult to use biologic methods of determination. These tests, as ordinarily performed in clinical laboratories, are so inaccurate that it is not worth while to do them routinely.

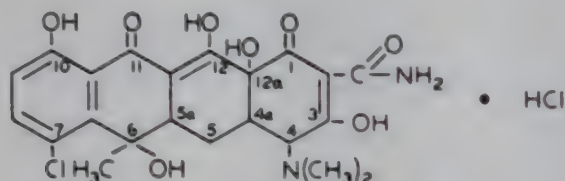
When a single moderate dose of aureomycin is administered orally, maximal absorption, as measured by its concentration in the blood serum, appears to occur in two to eight hours, and detectable quantities of the antibiotic are present in the blood serum for at least 12 hours. When multiple doses are given at 6-hour intervals, concentrations of 2.5 to 20 mcg. are found in the blood serum. Aureomycin has been found in emulsions of the liver, kidneys, spleen and lungs of patients who died during aureomycin therapy. It is suspected that the antibiotic actually diffuses into the intracellular water of these tissues. It is difficult to explain the action of aureomycin upon *Rickettsia* without assuming that it penetrates endothelial cells. This antibiotic does not easily pass the blood brain barrier in human beings, but, when infection of the meninges is present, it is possible to detect it in the cerebrospinal fluid. It passes into the bile in fair concentrations, but as yet it is not known whether it diffuses into the vitreous or aqueous humors. It passes the placental barrier, and appreciable amounts can be detected in the cord blood of the infant whose mother is receiving aureomycin.

Of a single dose of aureomycin, 12 to 15 per cent can be recovered from the urine in which it may be excreted for as long as 72 hours. Concentrations of several hundred micrograms of aureomycin are easily obtainable in the urine following moderate and repeated doses.

Maximal concentrations in the blood apparently are reached within five minutes following intravenous injection of aureomycin; and detectable amounts may be present for as long as 12 hours. It is of importance to the physician, when he is considering the use of aureomycin in critically ill patients, to know that small intravenous doses of aureomycin produce excellent blood concentrations.

**AUREOMYCIN HYDROCHLORIDE-U.S.P.**—The hydrochloride of 7-chloro-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydropentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide. — Aureo-

mycin is an antibiotic isolated from the elaboration products of *Streptomyces aureofaciens*, when the micro-organism is grown on suitable culture media. It complies with the requirements of the Federal Food and Drug Administration. The structural formula of aureomycin hydrochloride may be represented as follows:



**Physical Properties.**—Aureomycin hydrochloride is an odorless, yellow, crystalline powder with a bitter taste. It is stable in air and may be affected by light. It is soluble in solutions of the alkali hydroxides and their carbonates but practically insoluble in acetone, chloroform, dioxan and ether.

**Actions and Uses.**—In vitro, aureomycin hydrochloride is effective against certain strains of beta hemolytic streptococci, nonhemolytic streptococci group D, alpha hemolytic streptococci, pneumococci, staphylococci, *Escherichia coli*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Bacillus subtilis* and *Corynebacterium hoffmanii*. In embryonated eggs it kills rickettsiae and certain large viruses.

Clinically, aureomycin hydrochloride is effective in the treatment of Rocky Mountain spotted fever, typhus, scrub typhus, murine typhus, Q fever and Brills' disease in the rickettsial group; primary atypical pneumonia; beta hemolytic streptococcal infections, and urinary tract infections produced by *E. coli*, *A. aerogenes*, staphylococci or streptococci. Aureomycin is also effective in acute laryngo-tracheobronchitis, acute infectious croup (nondiphtheritic), acute bronchitis and bronchiolitis, acute anthrax, otitis media and actinomycosis. It may be used, with or without surgical therapy, for mastoiditis and for infections produced by *E. coli*, including urinary tract infections, peritonitis, meningitis and, with surgical therapy, for abscesses. Recommendations for use in acute extra-intestinal and intestinal amebic infections include amebic hepatitis and, with surgery, amebic abscess. For gonococcal infection, including acute gonorrheal ophthalmia, penicillin still appears to be the antibiotic of choice, but aureomycin has been reported to be very effective. Results with yaws seem to be about equal to those obtained with penicillin. It may also be used in staphylococcal and pneumococcal infections, in acute brucellosis and in subacute bacterial endocarditis produced by both gram-positive and gram-negative bacteria.

Aureomycin hydrochloride should not be used in systemic infections produced by *Proteus vulgaris* or *Pseudomonas aeruginosa*. Clinical reports seem to indicate that aureomycin hydrochloride is a beneficial therapeutic agent in the treatment of whooping cough. It is of limited value in typhoid fever, and its effect in other types of salmonella infections is questionable.

The drug, suitably buffered, may be used locally in the eye



against a variety of ocular viral infections, such as inclusion conjunctivitis, follicular conjunctivitis and ocular bacterial infections caused by susceptible organisms.

Aureomycin hydrochloride, in a suitably buffered solution, may be administered intravenously to hospitalized patients unable to take the drug by mouth. Because of the danger of thrombophlebitis at the site of injection, intravenous therapy should be discontinued as soon as oral administration can be resumed.

The drug produces nausea, vomiting and diarrhea in some patients.

**Dosage.**—The minimum daily oral dose for the average adult is 1 Gm. divided into four 0.25 Gm. doses. Children should receive proportionately less; for example, a 44-pound (about 20 Kg.) child may be given 50 mg. four or five times daily. In the absence of a clinical response within 24 hours or for acutely ill patients, the total number of daily doses (0.25 Gm.), rather than the size, should be increased on the second or third day, as individual doses exceeding 0.25 Gm. are not absorbed efficiently.

Solutions for ophthalmic use may be prepared by adding 5 cc. of sterile distilled water to 25 mg. of the hydrochloride. One or two drops in the affected eye every 2 hours usually suffices to control the condition.

A solution buffered with sodium glycinate, and containing not more than 100 mg. of aureomycin hydrochloride per 10 cc. of sterile diluent, is administered intravenously on the basis of 20 to 25 mg. per Kg. of body weight every 24 hours. This daily dosage should be divided into two, three or four injections given at intervals of 12, 8 or 6 hours, respectively, depending on the schedule indicated. Solutions should be prepared immediately before use and only water for injection-U.S.P., isotonic sodium chloride solution-U.S.P. or 5 per cent dextrose injection-U.S.P. should be used as a diluent. All of the diluent (10 cc. for each 100 mg.) should be injected into a sterile vial containing the drug and the buffer, and the contents shaken vigorously for at least 1 minute to insure solution prior to administration. To avoid reactions, approximately 5 minutes should elapse for the injection of each 10 cc. of solution.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

**Aureomycin Hydrochloride:** Vials with dropper containing 25 mg. of aureomycin hydrochloride, 62.5 mg. of sodium chloride and 25 mg. of sodium borate, to be diluted with distilled water for ophthalmic use.

**Capsules Aureomycin Hydrochloride:** 50, 100 and 250 mg.

**Ointment Aureomycin Hydrochloride (Ophthalmic) 1%:** 3.5 Gm. tubes. An ointment containing 10 mg. of aureomycin hydrochloride in each gram.

**Powder Aureomycin Hydrochloride (Intravenous):** 10 and 50 cc. vials. A powder containing 0.1 and 0.5 Gm., respectively, of aureomycin hydrochloride. Buffered with sodium glycinate.



**Spersoids Aureomycin Hydrochloride:** 36 and 75 Gm. bottles. A flavored powder containing 16.7 mg. of aureomycin hydrochloride in each gram.

**Soluble Tablets Aureomycin Hydrochloride:** 50 mg.

### Bacitracin

**BACITRACIN.**—Bacitracin consists of the antibiotic substance or substances produced by the growth of *Bacillus subtilis*, strain Tracy I. It complies with the requirements of the Federal Food and Drug Administration. The unit of bacitracin is equivalent to 26 mcg. of the Food and Drug Administration working standard.

**Actions and Uses.**—Bacitracin is a bactericidal antibiotic effective against a wide variety of gram-positive organisms, including hemolytic and nonhemolytic streptococci, staphylococci and pneumococci, anaerobic cocci and clostridia of the gas gangrene group, corynebacteria, the spirochetes of syphilis and those of the mouth, *Actinomyces israeli* and certain gram-negative cocci, including gonococci and meningococci. However, it is ineffective against most aerobic gram-negative bacilli. Bacitracin is indicated in the treatment of infections caused by susceptible organisms and is often successful when such infections have failed to respond to penicillin and other antibiotics. Its speed of bactericidal action is in direct proportion to its concentration. Bacitracin is eliminated from the body slowly; traces are present in the blood 6 to 8 hours after intramuscular injection. Patients are seldom, if ever, primarily sensitive to bacitracin, nor do they develop sensitivity to it following repeated courses of the antibiotic. Bacteria are very slow in developing resistance to bacitracin.

Bacitracin may be used by intramuscular injection in the treatment of systemic infections caused by organisms susceptible to the antibiotic and by local injection into circumscribed areas of infection, such as furuncles, carbuncles or abscesses, often obviating surgery. Either alone or in conjunction with intramuscular therapy, it has been used successfully and safely by the intrathecal, intraventricular, intracisternal or intracerebral injection in the treatment of susceptible neurosurgical infections, including osteomyelitis of the skull, septic coccal meningitis, brain abscess and postoperative infections. Bacitracin also is employed locally by topical application in water-soluble or petrolatum ointment bases or in aqueous or saline solutions in the treatment of infections of the skin, eye, nose and throat or in surgical infections of the soft parts and bone, as well as in the prophylactic and active treatment of infected burns. It has been used by inhalation for susceptible respiratory tract infections. Because it is not absorbed from the gastro-intestinal tract, oral use of large quantities does not result in detectable blood levels. Its oral use for intestinal amebic infection has been successful.

Bacitracin is a polypeptide, and the intramuscular injection of large doses may produce renal tubular swelling. With the smaller doses, traces of albumin usually appear in the urine starting on the second or third day, reach a low peak on the fifth to the seventh

day and usually fall again with continued treatment, indicating that the kidneys adapt themselves to its use. Along with the albuminuria, cellular elements in the urine usually increase and a few granular casts appear. Output of urine often is increased. With larger doses, these abnormalities are increased, and, occasionally, blood urea nitrogen rises. This may usually be obviated by making certain that fluid intake is adequate—for adults, 2,500 cc. a day and for children a corresponding amount. Other side effects include loss of appetite and, occasionally, nausea and vomiting. Urticaria is extremely rare. There may be some painful induration at the site of injection; therefore, to minimize or obviate any untoward side reactions when bacitracin is administered intramuscularly, care should be exercised not to exceed the maximum advocated dosage and to assure adequate intake of fluid (2,500 cc. a day).

Before intramuscular therapy is initiated, if the facilities are available, the urine should be examined for albumin, casts and cellular elements; blood determinations should be made for either urea nitrogen or nonprotein nitrogen. During the period of treatment, patients should be checked routinely for evidences of renal damage; the urine should be examined for albumin and cellular pathology every other day, and the blood checked weekly for evidence of retained nitrogen. However, the results of these examinations are not likely to be alarming if intake of fluid is adequate.

The fluid intake and urinary output should be measured carefully every day. This is the most important factor in respect to kidney function. If output remains above 1,000 cc., there need be little fear of toxicity. If it drops below 600 cc. with adequate intake, systemic bacitracin should be stopped. If there are no signs of toxicity in the first week, intramuscular administration may be continued as long as necessary to control the infection. In several instances it has been used continuously for months without evidence of cumulative toxicity; however, it usually can be discontinued safely 3 days after the temperature has returned to normal and all signs of infection have subsided. In the treatment of meningitis, the drug should be continued until the spinal fluid is clear and cultures do not show growth. Intramuscular injection should be used cautiously in patients with known impairment of renal function, even though it has not been observed that toxicity is more likely to develop in such patients than in those with normal kidney function. In some cases in which the infection itself was responsible for a high level of albuminuria and retention of nitrogen, bacitracin has controlled the infection and restored kidney function. The occurrence of mild nephrotoxicity does not necessarily contraindicate continued use of the drug, but it should be discontinued if there is evidence of progressive nitrogen retention or progressive diminution of urinary output. Nephrotoxicity has not been observed following local injection of bacitracin into the central nervous system or into areas of infection or after topical application to the skin, eye or respiratory tract.

**Dosage.**—In the treatment of systemic infections, bacitracin is administered by intramuscular injection. The total daily dose for adults should not exceed 100,000 units. The usual dose for adults



should start with 10,000 to 20,000 units every 8 hours. The initial dose for children is 200 units per kilogram of body weight administered at 8-hour intervals. If there is no response within 48 hours, the dose may be increased to a maximum of 25,000 units for adults or 400 units per kilogram of body weight for children, given every 6 hours. Procaine hydrochloride 2 per cent in isotonic sodium chloride solution may be used as a diluent for solutions injected intramuscularly, using a quantity sufficient to make a concentration of 10,000 units per cubic centimeter. Sites of intramuscular injection should be rotated to avoid painful induration.

In neurosurgical infections, bacitracin is administered by intrathecal, intraventricular, intracisternal or intracerebral injection by dilution with isotonic sodium chloride solution to make a concentration of 1,000 units per cubic centimeter. *Procaine should not be added to solutions for neural injection.* For patients 15 years of age and older, the daily dose by any of the stated intraneural routes is 10,000 units. For infants and young children, the daily dosage varies from 250 to 5,000 units, depending on the particular neural route and the age of the patient.

For infections of the peritoneal cavity, usually due to a mixture of intestinal organisms, 20,000 units of bacitracin in 20 cc. of isotonic sodium chloride solution may be instilled to combat the coccal and clostridial elements of the infection. The same amount may be sprayed over the operative field after resection of the bowel.

For oral administration in the treatment of intestinal amebiasis, an average daily dosage of 80,000 to 120,000 units is given in divided doses at 6-hour intervals (after meals and at bedtime) for a period of 2 weeks.

For topical application to the skin, instillation in the eye or injection of circumscribed areas of acute infection, the concentration should be 500 to 1,000 units of bacitracin per gram of ointment or per cubic centimeter of solution. Solutions containing 250 or 500 units per cubic centimeter can be employed topically to irrigate wet dressings or the drug may be applied in dry form as a dusting powder. A 1,000-unit per cubic centimeter solution may be diluted with equal parts of 2 per cent procaine hydrochloride for injection into acutely inflamed areas. For intranasal therapy, a solution containing 250 units per cubic centimeter is employed.

#### ABBOTT LABORATORIES

**Ointment Bacitracin:** 15, 30 and 113 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

**Ophthalmic Ointment Bacitracin:** 4 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

#### COMMERCIAL SOLVENTS CORPORATION

**Ointment Bacitracin:** 14.2 and 28.4 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.



Ophthalmic Ointment Bacitracin: 3.54 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

#### ELI LILLY & COMPANY

Ointment Bacitracin: 15, 30 and 120 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Ophthalmic Ointment Bacitracin: 7 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Solvets Bacitracin: 2,500 units.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Bacitracin (*Parenteral*): 50,000 unit vials.

Bacitracin (*Topical*): 50,000 unit vials.

Ointment Bacitracin: 14.2 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Ophthalmic Ointment Bacitracin: 3.5 Gm. tubes. An ointment containing 500 units of bacitracin in each gram.

Soluble Tablets Bacitracin: 5,000 units.

#### THE UPJOHN COMPANY

Bacitracin (*Topical*): Vials. Powder containing the equivalent of 2,000, 10,000 or 50,000 units of bacitracin.

## Carbomycin

**CARBOMYCIN.**—Magnamycin (PFIZER).—Carbomycin is an antibiotic isolated from the elaboration products of *Streptomyces halstedii*, when grown by deep culture in suitable media. The structural formula of carbomycin has not been established.

**Physical Properties.**—Carbomycin is a white, odorless, bitter powder, with a melting point between 195 and 220° (with decomposition). It is freely soluble in chloroform and very slightly soluble in water. The approximate amounts which dissolve at 25° in the following solvents to form 100 ml. of solution are: 4 Gm. in alcohol and 0.9 Gm. in ether. Carbomycin is stable when protected from moisture. The pH of a saturated solution is 5.5 to 8.0.

**Actions and Uses.**—Carbomycin, a monobasic antibiotic of incompletely defined chemical identity, possesses strong inhibitory activity against certain gram-positive bacteria. Its activity against other types of bacteria and other micro-organisms is under investigation. Until adequate clinical evidence becomes available, carbomycin is indicated only in the treatment of infections caused by staphylococci, pneumococci and hemolytic streptococci. Therefore, it is useful in the treatment of pneumonia, urinary tract infections, soft tissue infections, abscesses and tonsillitis caused by these

organisms. Its usefulness in bacteremia and septicemia has not been completely evaluated, but it can be employed in these conditions also when the causative organisms are found to be susceptible on the basis of sensitivity tests.

Carbomycin, as the free base, is only slightly soluble in water but is readily absorbed following oral administration. Blood levels produced following oral administration are not significantly lower than when water-soluble acid salts of the drug are administered by intramuscular injection. An appreciable amount (approximately 10 per cent of the ingested dose) is excreted in the urine in active form, and the drug appears to be distributed throughout the body in all organs and secretions. Following intravenous administration of its soluble salts, the drug disappears rapidly from the blood stream. The ultimate disposition in the body of the unexcreted portion has not been determined.

Carbomycin exhibits a low degree of toxicity in experimental animals. Clinically, no harmful side effects have been observed with therapeutically effective doses. Studies of the urine, blood and liver function have revealed no evidence of toxic action. Nausea and vomiting are the principal side effects; diarrhea occurs infrequently. As for all new drugs, close clinical observation for undiscovered toxic effects is desirable, and, for periods of therapy extending beyond 2 weeks, repeated blood counts should be performed. As with other antibiotics, its use may result in overgrowth of nonsusceptible organisms, particularly monilia. If new infections caused by nonsusceptible bacteria or fungi appear during therapy, the drug should be discontinued and/or appropriate measures instituted.

**Dosage.**—Carbomycin is administered orally; optimal dosage is still under investigation. For adults, the present total daily dosage is 2 Gm. divided into four equal doses given every 6 hours; in urinary tract infections and in some soft tissue infections, 1 Gm. daily may be adequate. When infections do not respond to 0.5 Gm. every 6 hours, the dosage may be increased to 1 Gm. every 6 hours. Duration of therapy is governed by the clinical response and should be continued until temperature, pulse and respiration have been normal for 48 hours and until other acute manifestations have subsided. Dosage for children is also under study; carbomycin presently is given on the basis of 50 to 100 mg. per kilogram of body weight daily, divided into four equal doses administered at 6-hour intervals.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

Tablets Magnamycin: 0.1 Gm.

## Chloramphenicol

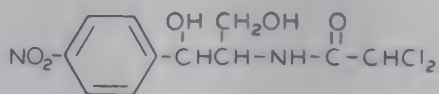
Chloramphenicol is a crystalline nitrobenzene compound now produced synthetically. It is relatively insoluble and, for that reason, usually administered by the oral route. Following a single



moderate oral dose of chloramphenicol, maximal blood concentration of the antibiotic is reached within 2 hours; the agent is not detectable in the blood after 8 hours. When multiple doses of chloramphenicol are given, little difficulty is encountered in maintaining high concentrations of the antibiotic in both the blood and the urine. Chloramphenicol appears to be well distributed in the body tissues. It undoubtedly is present in intracellular as well as extracellular body water, since otherwise it would not be so effective in the control of rickettsial infections. It passes over readily into the cerebrospinal and pleural fluids, and appreciable quantities are found in the bile. The placenta offers no barrier to its passage, and the concentration of chloramphenicol in cord blood is approximately 75 per cent of that in the maternal blood within 2 hours after the administration of a single dose. It is as yet unknown whether chloramphenicol passes into the vitreous or aqueous humors. Chloramphenicol is excreted mainly in the urine, in which appreciable quantities appear within 30 minutes after administration of a single dose.

There are both chemical and biologic tests for the detection of chloramphenicol and its degradation products in body fluids and tissues. Comparison of the two tests on like samples of blood from patients who are receiving chloramphenicol shows that, for the first few hours after the antibiotic has been administered, the tests give comparable results. After this, however, the chemical values rise and the biologic values drop, indicating the conversion of chloramphenicol to an inactive form in the body. In the urine, this difference is always great, the chemical test giving readings about ten times greater than those of the biologic test, another indication that the majority of chloramphenicol which has been excreted is in an inactive form. There is no evidence that renal dysfunction impairs the excretion of chloramphenicol in the urine.

**CHLORAMPHENICOL-U.S.P.—Chloromycetin (PARKE, DAVIS).—**D-(-)Threo-1-(*p*-nitrophenyl)-2-dichloroacetamido-1,3-propanediol.—The structural formula of chloramphenicol may be represented as follows:



**Physical Properties.**—Chloramphenicol occurs as fine, white to grayish-white or yellowish-white, needlelike crystals or elongated plates. It is bitter to taste, practically neutral to litmus paper and reasonably stable in neutral or moderately acid solutions. Its alcohol solution is dextrorotatory and its ethyl acetate solution is levorotatory. One gram of chloramphenicol is soluble in about 400 ml. of water and freely soluble in alcohol, in propylene glycol, acetone and ethyl acetate. It melts between 149 and 153°.

**Actions and Uses.**—Chloramphenicol is an antibiotic derived from *Streptomyces venezuelae* or produced synthetically. It is ef-



fective against certain gram-negative organisms and against Rickettsia.

Because of the occurrence of serious and fatal blood dyscrasias, it is advisable to restrict the use of chloramphenicol to the treatment of typhoid fever and other serious infectious diseases caused by organisms controlled by chloramphenicol but resistant to other antibiotics or other forms of treatment.

The drug is rapidly absorbed from the gastro-intestinal tract and appears promptly in the blood stream after a single oral dose. It is excreted in the urine in high concentration, about 10 per cent being in the active form. The concentration in the spinal fluid is about half of that in the blood.

Chloramphenicol may produce nausea and vomiting.

**Dosage.**—Initial oral doses of 50 to 75 mg. per kilogram of body weight are usually employed. Thereafter a dose of 0.25 Gm. may be given every 2 to 3 hours. In severe infections, this dose may be increased to 0.5 Gm. every 3 hours. The drug should be continued until the temperature is normal and the symptoms have subsided; it may then be given less frequently. In most infections, if the temperature remains normal the drug can be discontinued after 48 hours.

PARKE, DAVIS & COMPANY

**Capsules Chloromycetin:** 50 and 100 mg.

**Kapseals Chloromycetin:** 0.25 Gm.

**Ophthalmic Ointment Chloromycetin 1%:** 3.54 Gm. tubes. An ointment containing 10 mg. of chloramphenicol in each gram.

**Ophthalmic Solution Chloromycetin (Dried):** 25 mg. vials. A powder containing 25 mg. of chloramphenicol and borate buffer equivalent to 100 mg. of boric acid in each vial. To be diluted with distilled water.

U. S. patents 2,483,871, 2,483,884, 2,483,885, 2,483,892.

## Erythromycin

**ERYTHROMYCIN.**—**Ilotycin (LILLY).**—Erythromycin is an antibiotic isolated from the elaboration products of *Streptomyces erythreus*, when grown by deep culture in suitable media. The structural formula of erythromycin has not been established.

**Physical Properties.**—Erythromycin is a white or slightly yellow, odorless, bitter, crystalline powder, with a melting point between 133 and 138°. It is freely soluble in alcohol and ether and very slightly soluble in water. Erythromycin is slightly hygroscopic. The pH of a saturated solution is 8.0 to 10.5.

**Actions and Uses.**—Erythromycin is clinically effective against certain infections caused by gram-positive bacteria. These include certain beta-hemolytic streptococci, pneumococci and staphylococci. Bacteriologic studies have shown that erythromycin is similar to

penicillin in antibacterial activity. However, at present, there is insufficient clinical evidence to warrant the use of erythromycin against other gram-positive micro-organisms such as alpha-hemolytic and nonhemolytic streptococci or against gram-negative bacteria such as meningococci and gonococci. Bacterial resistance to erythromycin may develop rapidly. The drug is as active against susceptible penicillin-resistant strains as it is against penicillin-sensitive strains.

Erythromycin may produce mild gastro-intestinal disturbances. Thus far, such side effects are infrequent and seem to be related to dosage; large doses occasionally cause nausea, vomiting, diarrhea and prostration. Erythromycin does not induce the profound change in intestinal flora encountered with prolonged use of broad-spectrum antibiotics. Contraindications thus far have not developed, but until there has been longer experience in its use, physicians should be alert to the appearance of untoward reactions. When therapy is prolonged more than 2 weeks, repeated blood counts are advisable.

**Dosage.**—Erythromycin is currently administered only by the oral route. With specially coated tablets, the drug may be taken with meals. In this form, a single dose of 0.2 Gm. produces an average blood concentration of 0.04 to 0.16 mcg. per cubic centimeter for 6 to 8 hours.

Optimal dosage has not been finally established. The average effective dosage for adults ranges from 0.2 to 0.5 Gm. every 6 hours; for children, doses of 6 to 8 mg. per kilogram of body weight every 6 hours are suggested. *Pneumococcus pneumonia* has responded to doses of 0.2 Gm. initially and 0.1 Gm. every 3 hours. In severe infections, doses up to 0.5 Gm. may be repeated every 6 hours if necessary. Doses in excess of 0.5 Gm., administered every 6 hours, occasionally have produced nausea, vomiting and diarrhea.

ELI LILLY & COMPANY

Tablets Ilotycin (*Specially Coated*): 0.1 Gm.

**ERYTHROMYCIN STEARATE.**—Erythrocin Stearate (ABBOTT).—Erythromycin stearate is the stearic acid salt of erythromycin. It usually contains some uncombined stearic acid. The structural formula of erythromycin stearate has not been established.

**Physical Properties.**—Erythromycin stearate is a bulky, white powder having a slight musty odor. It is freely soluble in alcohol and practically insoluble in water. About 5 Gm. of erythromycin stearate dissolves in 100 ml. of ether.

**Actions and Uses.**—Erythromycin stearate has the same actions and uses as erythromycin base. (See the monograph on erythromycin.) The stearate salt, when properly buffered, gives blood levels comparable to those obtained with the base.

**Dosage.**—Erythromycin stearate is administered orally. The dosage is expressed in terms of, and is identical with, the base. (See the monograph on erythromycin.) For children, the recommended dose is 4.5 to 6.5 mg. of erythromycin base per kilogram



(2 to 3 mg. per pound) of body weight, administered at 4-hour to 6-hour intervals.

#### ABBOTT LABORATORIES

**Oral Suspension Erythrocin Stearate (*Pediatric*):** 60 cc. bottles. A flavored suspension containing 20 mg. of erythromycin as the stearate in each cubic centimeter. Preserved with 0.1 per cent methylparaben and 0.02 per cent propylparaben.

### Neomycin

**NEOMYCIN SULFATE.**—**Mycifradin Sulfate (UPJOHN).**—Neomycin is an antibiotic isolated from the elaboration products of *Streptomyces fradiae*, when the micro-organism is grown on suitable culture media.

**Actions and Uses.**—Neomycin sulfate is a polybasic compound, thermostable and soluble in water but insoluble in organic solvents. It differs from other antibacterial agents in that it is extremely stable and very active in alkaline solution. Neomycin is not inactivated by exudates, enzymes, gastro-intestinal secretions and by-products of digestion or bacterial growth. The sulfate salt is stable in the dry state for at least 2 years when stored at room temperature. Prepared solutions retain their potency for at least 1 year at room temperature, although there may be a progressive deepening of color of solutions stored at room temperature or 37°. Refrigeration of neomycin solutions is, therefore, recommended.

Neomycin sulfate exhibits activity against a variety of gram-positive and gram-negative bacteria. In the former group, it appears to be more effective against staphylococci than streptococci. It has a wider antibacterial spectrum than bacitracin, penicillin or streptomycin, and it is sometimes effective against *Pseudomonas* and *Proteus* infections. Micro-organisms resistant to neomycin have been demonstrated in vitro, but emergence of resistant strains has not yet been observed clinically. It may be effective against micro-organisms that have developed resistance to streptomycin; however, the evidence thus far available does not justify the conclusion that neomycin suppresses the overgrowth of resistant bacterial variants. It is not active against fungi.

Neomycin sulfate is useful for topical application as a solution or ointment in the local treatment or prevention of susceptible infections of the skin and the eye, including pyogenic or secondarily infected stasis dermatoses, impetigo, wounds, burns, ulcers (varicose or trophic), conjunctivitis, blepharitis and sty (hordeolum). A solution is considered superior to an ointment in treating trophic ulcers and secondarily infected burns. In severe or extensive infections, local therapy should be supplemented with sulfonamides by mouth or penicillin by injection.

Neomycin sulfate is also useful as an intestinal antiseptic by oral administration for suppression of the usual bacterial inhabitants of the colon in surgery of the large bowel and anus. Because of its poor absorption from the gastro-intestinal tract, it rarely produces



systemic action or toxic effects when administered orally. The small fraction absorbed (about 3 per cent of the amount ingested) is rapidly excreted in the urine; the remainder is excreted unchanged in the feces. Divided total daily oral dosage not exceeding 6 to 10 Gm. for 1 to 3 days produces blood levels lower than the toxic serum concentration of 0.2 mg. per cubic centimeter which occurs with parenteral injection. Blood levels of this concentration may produce serious kidney damage. *Therefore, neomycin should not be injected parenterally, and when given orally, high dosage and prolonged administration should be avoided to prevent possible systemic effects.* Outgrowth of nonpathogenic yeasts usually follows reduction of the bacteria flora of the colon; *Aerobacter aerogenes* may grow out about 12 hours following the outgrowth of yeasts. The effectiveness of neomycin is variable in suppressing organisms of the clostridia group.

Neomycin sulfate is usually well tolerated and is relatively non-irritating. It is reported to have a low index of sensitization. A mild laxative effect occurs with oral administration. Prolonged oral therapy may result in overgrowth of nonsusceptible organisms—particularly *Candida*. If new infections caused by bacteria or fungi appear during therapy, it may be advisable to discontinue the drug and/or institute appropriate measures to combat them. Oral use as an intestinal disinfectant is contraindicated in the presence of obstruction.

**Dosage.**—Neomycin sulfate is applied topically or administered orally for its local action in the large intestine.

For external use, it is applied as a solution containing 5 mg. per cubic centimeter or as an ointment containing 5 mg. per gram. The solution is used for wet dressings, packs, irrigations or instillation. Topical applications of the solution or ointment are made once or twice daily, using an amount sufficient to cover the affected region.

For preoperative disinfection of the colon, the patient is placed on a low residue diet and, immediately following the administration of a cathartic (unless otherwise contraindicated), is given an oral dose of 1 Gm. every hour for four doses followed thereafter by 1 Gm. every 4 hours for 24 to 72 hours prior to surgery. Administration of the antibiotic should not extend beyond 72 hours. This amount usually produces four to eight bowel movements.

#### ELI LILLY & COMPANY

**Ointment Neomycin Sulfate:** 14.2, 28.35 and 113.4 Gm. tubes. An ointment containing 5 mg. of neomycin sulfate in each gram.

**Ophthalmic Ointment Neomycin Sulfate:** 3.54 Gm. tubes. An ointment containing 5 mg. of neomycin sulfate in each gram.

#### THE UPJOHN COMPANY

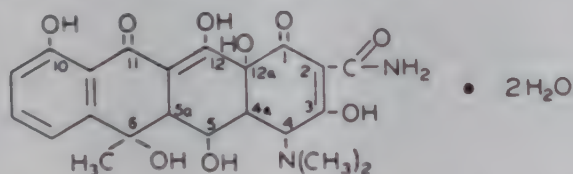
**Powder Mycifradin Sulfate:** Vials containing 0.5 Gm. of neomycin sulfate.

**Tablets Mycifradin Sulfate:** 0.5 Gm.

## Oxytetracycline (Terramycin)

At present there is no chemical test for measuring oxytetracycline in the body fluids or tissues. Hence, studies of its absorption, distribution and excretion in human beings are based on data derived from biologic tests which are only relatively accurate. When administered orally, oxytetracycline is absorbed promptly; there are appreciable concentrations in the blood up to 24 hours after a single dose of 2 Gm. A schedule based on a 6-hour interval between doses is satisfactory for the maintenance of adequate concentrations in the blood. The antibiotic appears in emulsions of most of the organs of animals which have been given standard therapeutic doses, and it is believed that it diffuses into cells. Oxytetracycline is sometimes detected in the spinal fluid following administration to normal individuals, particularly if the meninges are inflamed. It diffuses into pleural and abdominal fluids, and passes the placental barrier easily. High concentrations of a biologically active form are excreted in the bile, stool and urine. There is no evidence that renal dysfunction interferes with the excretion of oxytetracycline. Metabolic studies of the degradation of oxytetracycline in the body have not yet been reported.

**OXYTETRACYCLINE.**—Terramycin (PFIZER).—The dihydrate of 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide. — Oxytetracycline is isolated from the elaboration products of the actinomycete, *Streptomyces rimosus*, when the micro-organism is grown on suitable culture media. The structural formula of oxytetracycline may be represented as follows:



**Physical Properties.**—Oxytetracycline is a dull yellow, odorless, slightly bitter crystalline powder. It melts between 179 and 182° (with decomposition). It is soluble in acids and alkalis, very slightly soluble in acetone, alcohol, chloroform and water and practically insoluble in ether.

**Actions and Uses.**—Oxytetracycline, as the base, is suitable for oral administration for the same purposes as the more soluble oxytetracycline hydrochloride. (See the general statement on oxytetracycline and the monograph on oxytetracycline hydrochloride.) Clinical studies of serum levels indicate that absorption of the base is approximately comparable to that of the hydrochloride following oral administration of equal doses of either form. Significant differences in side reactions have not been observed.

**Dosage.**—Oxytetracycline, as the base, is administered in the same doses as specified for oxytetracycline hydrochloride, since the



latter is also expressed in terms of the base. See the monograph on oxytetracycline hydrochloride.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

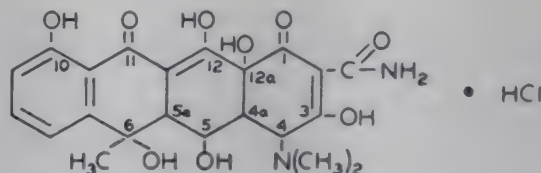
**Pediatric Drops Terramycin:** 1 Gm. vials. A powder with added flavoring for suspension in water to give a solution containing 100 mg. of oxytetracycline in each cubic centimeter.

**Oral Suspension Terramycin:** 1.5 Gm. vials. A powder with added flavoring for suspension in distilled water to give a solution containing 50 mg. of oxytetracycline in each cubic centimeter.

Tablets Terramycin: 50 mg., 0.1 Gm. and 0.25 Gm.

U. S. trademark 577,504.

**OXYTETRACYCLINE HYDROCHLORIDE.**—Terramycin Hydrochloride (PFIZER).—Hydrochloride of 4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide.—Oxytetracycline is an antibiotic isolated from the elaboration products of the actinomycete, *Streptomyces rimosus*, when the micro-organism is grown on suitable culture media. The structural formula of oxytetracycline hydrochloride may be represented as follows:



**Physical Properties.**—Oxytetracycline hydrochloride is a yellow, crystalline, odorless powder with a bitter taste. It melts with decomposition between 190 and 194°. It is very soluble in water, soluble in alcohol, sparingly soluble in acetone, slightly soluble in chloroform and very slightly soluble in benzene and ether. The pH of a 1 per cent solution of oxytetracycline hydrochloride is about 2.5.

**Actions and Uses.**—Oxytetracycline hydrochloride exercises bacteriostatic or bactericidal effect depending on its concentration. It is active in vitro against certain strains of Beta hemolytic streptococci, Alpha hemolytic streptococci, nonhemolytic streptococci, pneumococci, staphylococci, *Escherichia coli*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Hemophilus influenzae* and a number of other micro-organisms. It is not very effective in this respect against certain strains of *Pseudomonas aeruginosa* or *Bacillus proteus*.

Oxytetracycline hydrochloride has proved effective in the clinical treatment of various bacterial infections: staphylococcic and Beta hemolytic streptococcic infections, including urinary tract infections produced by certain strains of *E. coli*, *A. aerogenes*, streptococci or staphylococci, Bacteroides infection, brucellosis and pneumococcic pneumonia. Clinical reports seem to indicate that oxytetracycline hydrochloride is a beneficial therapeutic agent in



the treatment of whooping cough. It is not very effective for treatment of bacterial infections produced by *Ps. aeruginosa*, *B. proteus*, or organisms of the Salmonella group and it is not effective in typhoid fever. Oxytetracycline hydrochloride may also be used preoperatively and postoperatively in surgical procedures on the large bowel to suppress the normal colonic bacterial flora. Although beneficial in gonorrhea, penicillin is the antibiotic of choice. Oxytetracycline hydrochloride is effective against rickettsial infections in the treatment of Rocky Mountain spotted fever, typhus, scrub typhus, rickettsial pox and Q fever. It is also effective in viral and viral-like infections of primary atypical pneumonia, lymphogranuloma venereum, acute trachoma and granuloma inguinale. The role of the drug in the control of other virus infections is being evaluated. Oxytetracycline hydrochloride is effective against the protozoan diseases of amebiasis, yaws and syphilis, but penicillin is the antibiotic of choice for the treatment of syphilis.

The drug is administered orally, but suitably buffered preparations may be used locally for the treatment of ocular infections produced by susceptible bacteria or viruses. It may also be administered intravenously in severe infections which are susceptible to the drug.

Oxytetracycline hydrochloride produces nausea, vomiting, diarrhea, skin rashes or drug fever in some patients. Because it actively suppresses the growth of many bacteria, oxytetracycline permits their replacement by growths of yeastlike organisms; thus thrush or other forms of moniliasis may develop in patients receiving the drug.

**Dosage.**—The dosage of oxytetracycline hydrochloride required to produce optimum therapeutic response will vary from one patient to another, depending upon the severity, response and susceptibility of the infection. In the average adult, the suggested minimum daily dose should be 1 Gm. Higher daily doses (2 Gm.) are required for severe infections or for those patients who do not respond rapidly to lower dosages. As much as 4 Gm. daily is well absorbed and tolerated in the treatment of patients with very severe infections. The total daily dose should be administered in four equal portions given at 6-hour intervals. Administration of oxytetracycline hydrochloride with cold milk or a light meal helps to increase upper gastro-intestinal tract tolerance. The total daily dose for children is proportionately less than for adults. In severe infections in children, 25 to 40 mg. per kilogram of body weight daily should be adequate.

As a guide to therapy, the high urinary and intestinal concentrations of oxytetracycline hydrochloride following oral administration and the stability of oxytetracycline hydrochloride in the body fluids should be taken into consideration.

Duration of therapy should be for at least 24 or 48 hours after symptoms and fever have subsided.

Certain diseases are treated in courses, such as 10 days for intestinal amebiasis; subacute bacterial endocarditis requires therapy for long periods of time, such as 6 to 8 weeks, the duration of

treatment being guided by bacteriologic and clinical response with appropriate follow-up observations. One gram, administered in two 0.5 Gm. doses at 6-hour intervals, is sufficient to cure 98 per cent of acute gonococcal infections.

Intravenous therapy should not be used beyond the point at which the patient can accept oral medication, nor should the intravenous route be employed in the treatment of mild infections. The drug should not be administered subcutaneously or intramuscularly, but in highly localized infections, which cannot be penetrated by the blood stream, small quantities may be injected directly into the infected area.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

**Capsules Terramycin Hydrochloride:** 50 mg., 100 mg. and 250 mg. Each capsule contains the equivalent of 50 mg., 100 mg. or 250 mg., respectively, of oxytetracycline as the hydrochloride.

**Terramycin Hydrochloride (*Intravenous*):** Vials containing the equivalent of 0.25 Gm. and 0.5 Gm. of oxytetracycline as the hydrochloride. Buffered with 0.23 Gm. and 0.45 Gm. of sodium glycinate, respectively.

**Ophthalmic Solution Terramycin Hydrochloride:** Bottles containing the equivalent of 25 mg. of oxytetracycline as the hydrochloride with 62.5 mg. of sodium chloride. Buffered with 25 mg. of sodium borate. To be diluted with 5 ml. of distilled water.

**Oral Drops Terramycin Hydrochloride:** 10 cc. dropper bottles. A flavored alcohol solution containing the equivalent of 0.2 Gm. of oxytetracycline as the hydrochloride in each cubic centimeter (approximately 50 mg. in each 9 drops). The oxytetracycline hydrochloride and diluent are packaged together in separate containers to be mixed before using.

U. S. patent 2,516,080. U. S. trademark 577,504.

## Penicillin

Penicillin is an antibiotic substance, existing in several forms, that is derived from certain species of molds belonging to the genus *Penicillium* by extraction of cultures grown on special media. The various forms of penicillin, so far isolated, have been designated as F, G, K, O and X.

Amorphous mixtures formerly were widely employed in the form of their sodium or calcium salts. Crystalline preparations of greater purity and stability, containing more than one kind of penicillin or containing chiefly penicillin G as either the sodium or potassium salt, are now used in the majority of instances. Penicillin O is allylmercaptomethyl penicillin produced by growing the mold in a medium containing allylmercaptoacetic acid.

Penicillin mixtures for parenteral or oral use are limited by the Food and Drug Administration to a content of not more than 30 per cent of penicillin K. Topical forms are not restricted as to



content. Crystalline penicillin is defined by the Food and Drug Administration as the heat-stable crystalline (sodium or potassium) salt of one or more kinds of penicillin; it must be capable of withstanding exposure to 100° for 4 days. Amorphous and crystalline mixtures are required to have a potency of not less than 500 units per milligram. Crystalline preparations designated as Crystalline Penicillin G are required to contain 90 per cent of G, determined by the N-ethylpiperidine method; the sodium salt to have a potency of not less than 1,500 units per milligram; the potassium salt a potency of not less than 1,435 units per milligram. One unit is defined as the penicillin activity contained in 0.6 mcg. of the Food and Drug Administration master standard and is approximately equivalent to the original Oxford unit. Potency is assayed by bacteriologic testing against a strain of *Staphylococcus aureus* or other suitable organism.

When given orally by no means all of the penicillin or all of its metabolites are recovered from the urine. Studies in which penicillin has been "tagged" with radioactive sulfur demonstrate that the limited excretion of penicillin or its metabolites is due to incomplete absorption from the gastro-intestinal tract. This means that a considerable amount of penicillin may be excreted in the stool. This observation coupled with those which show that penicillin, except in the form of the complex salt benzathine penicillin G, is destroyed by gastric juice in the stomach and by penicillinase produced by many strains of *E. coli* in the large bowel, make it clear that the administration of penicillin by the oral route is an uncertain therapeutic procedure.

When aqueous solutions of crystalline penicillin G are administered by the intravenous route, peak concentrations are reached in the blood in a few minutes, and then the blood levels begin to fall. Following intramuscular injection, maximal concentrations are reached in 30 to 60 minutes. Subcutaneous injections are absorbed at a more variable rate, but peak concentrations are generally reached in about 60 minutes. Following the injection of penicillin by any of these routes, maximal concentrations are quickly reached, and the blood level of the antibiotic falls rapidly if renal function is normal. Only traces may be found within 3 or 4 hours after injection. For this reason, a 3-hour schedule ordinarily has been advised for intramuscular administration of crystalline penicillin G, and 2-hour schedules seem advisable in the treatment of certain patients.

Penicillin given by inhalation is absorbed rapidly and curves of its concentration in the blood resemble those observed following intramuscular injection. Systemic diffusion of crystalline penicillin administered by the intrathecal, intrapleural or intrapericardial routes is much slower, and easily detectable quantities of the antibiotic may be found in the spinal, pleural or pericardial fluid for 12 to 24 hours after single doses. This is also true when penicillin is injected into synovial cavities, but apparently is not the case when it is injected into the peritoneal cavity, from which it is absorbed rapidly. Some diffusion into the blood may occur after



intranasal instillation of penicillin, and small amounts are absorbed from certain other mucous membranes.

Penicillin is therapeutically active when it combines with the albumin fraction of plasma proteins; it is not known whether this combination is chemical or physical. Penicillin does not diffuse into brain, nerve, bone and certain other tissues in appreciable amounts, and very little is found in the red blood cells. In normal individuals the diffusion of penicillin into the spinal fluid is very slow and irregular. Often after days of therapy, penicillin cannot be detected in the spinal fluid. It passes slowly into synovial, pleural and pericardial fluids, and rarely does its concentration in these fluids equal that which occurs concomitantly in the blood. Penicillin diffuses readily into ascitic fluids, where it reaches concentrations comparable to those in the blood. It passes easily from maternal to fetal blood and detectable quantities are found in the amniotic fluid. It does not pass readily into the vitreous or aqueous humors, nor into pus in abscesses. Penicillin appears to penetrate fibrin clots in concentrations similar to those in the blood. Penicillin is distributed in quantities corresponding to the content of extracellular water.

If renal function is normal, 90 to 100 per cent of crystalline penicillin G and its degradation products may be found in the urine within a few hours after a single intramuscular dose. It is important for the physician to keep in mind that, of the penicillin excreted in the urine, only 40 to 70 per cent may be biologically active, while the remainder is made up of its inactive metabolites. Penicillin is also excreted in the bile and a small amount is probably excreted in the stool. Little penicillin is excreted in the saliva, sweat, milk or tears. In patients with dehydration, cardiac failure, dropsy or impaired renal function, excretion of penicillin is retarded. If renal function is severely impaired, as in patients with anuria, penicillin accumulates in the blood, but the concentration drops rapidly as soon as the anuria is relieved. Acute toxic reactions in man from the accumulation of penicillin in the blood have never been reported.

Because penicillin is rapidly excreted by the kidneys by complete clearance, in a manner similar to that of iodopyracet or aminohippuric acid, numerous attempts have been made to decrease its rate of excretion. Iodopyracet injection, *p*-aminobenzoic acid, *p*-aminohippuric acid and other substances have been used for this purpose. The most practical compound has been probenecid, which inhibits reversibly a renal tubular transport mechanism by which penicillin is excreted, thus prolonging retention of penicillin in the blood, and permits easier maintenance of therapeutic concentrations in the plasma of the antibiotic. To achieve this effect, probenecid must be given concomitantly with penicillin in small oral doses administered at 6-hour to 8-hour intervals. Drug sensitivity to probenecid has been reported.

Probably the most widely used method for producing sustained concentrations of penicillin in the blood and urine is injection of

preparations of small particulate procaine penicillin G. The water-solubility of this salt of penicillin is about 0.7 per cent, and following the intramuscular injection of 300,000 units of suitable water suspension, detectable concentrations of penicillin are found in the blood of most subjects for at least 8 to 12 hours. In tests on human subjects, urine concentrations of penicillin lasted as long as 72 hours after single intramuscular injections of 300,000 units of procaine penicillin. Detectable amounts of penicillin are found in the blood of test subjects for at least 60 hours after the injection of 300,000 units of procaine penicillin suspended in peanut or sesame oil to which 2 per cent aluminum monostearate has been added. Furthermore, preparations of aluminum penicillinate suspended in peanut oil produce the same type of sustained concentrations of penicillin in the blood. Excretion of the antibiotic in the urine continues for a number of days after intramuscular injection of either of the latter two preparations. Physicians should keep in mind that preparations of small particulate crystalline procaine penicillin G are to be used when it seems desirable to prolong a given effective penicillin level. Increased dosage of procaine penicillin in aqueous suspension may increase the magnitude of penicillin concentration as well as prolong the penicillin effect.

### *Penicillin for Inhalation*

Penicillin liquid aerosol or dust may be inhaled through the nose or mouth for local application of the drug to the respiratory tract as an adjunct in the treatment of penicillin-susceptible infections encountered in sinusitis, laryngitis, tracheobronchitis, bronchiectasis, bronchial asthma and lung abscess. This route is of value when continued systemic administration is not feasible or when it is desired, in conjunction with systemic therapy, to produce a higher concentration of the drug at the site of infection. Inhalation should not be employed in lieu of adequate systemic therapy for acute infections. In sinus infection it should be employed only when negative pressure can be produced intermittently. Soluble aerosol penicillin produces therapeutic blood levels that may be adequate for the treatment of chronic pulmonary infections susceptible to the drug. Only penicillin mist is suitable for the supportive treatment of lung abscess. Dust penicillin is not recommended for adjunctive inhalation therapy of lung abscess or for the treatment of nasal, pharyngeal or oral infections.

The possibility of sensitivity to penicillin necessitates special caution in the use of inhalation therapy, particularly in patients with asthma or history of allergy. Because of the physical effect of dust, this form of penicillin is more likely to produce bronchospasm than is aerosol penicillin. If dust is used, however, particles of 20 to 40  $\mu$  are preferable to smaller particles since they have less tendency to cause bronchospasm or to be lost through exhalation. Dust penicillin produces sore throat and other local reactions in the mouth oftener than aerosol penicillin, but its greater convenience for short periods of therapy, particularly in



ambulant patients, makes it useful for the management of certain chronic infections. Dust penicillin, because of its tendency to induce bronchospasm, should be employed in infectious asthma only in carefully selected patients, and should not be employed in the presence of pulmonary emphysema or fibrosis.

**Dosage.**—As an aerosol, 1 to 2 cc. of a solution containing 25,000 to 50,000 units of penicillin per cubic centimeter may be nebulized and inhaled every 3 to 4 hours. As a dust, 100,000 units are inhaled one to three times daily by means of a suitable device. Inhalation of dust penicillin over a long period increases untoward reactions attributable to contact of the drug with the mucous membranes of the throat and mouth.

### *Penicillin for Oral or Sublingual Administration*

Penicillin G or O may be administered orally. However, because the drug is partially inactivated by the gastric juice and by certain bacterial enzymes in the lower bowel, it is necessary to use large amounts to achieve significant blood levels. Furthermore, absorption from the gastro-intestinal tract is irregular, hence oral administration requires doses of approximately five times the amount usually recommended for injection. Oral doses should be given between meals, preferably buffered with a suitable antacid such as sodium citrate, dihydroxy aluminum aminoacetate or aluminum hydroxide, although this may be unnecessary with crystalline products prepared in a suitable physical state or with tablets of aluminum penicillin. Soluble penicillin salts may also be added to the milk formulas of infants.

Soluble forms are also suitable for sublingual administration to persons who have difficulty in swallowing tablet forms. (Soluble preparations are listed under Penicillin for Inhalation.) However, oral administration of penicillin G or O is recommended only in special instances.

In order to secure effective blood levels of penicillin by the oral route over a more protracted period of time, special esters of penicillin are being utilized or probenecid is administered simultaneously.

**Dosage.**—Potassium penicillin G or O or aluminum penicillin may be administered orally (intermittent or continuous infusion). In general the dosage varies with the type and severity of the infection, but oral administration of the drug in most cases should be reserved for less severe conditions. For streptococcal infections without bacteremia, pneumococcal infections, or minor staphylococcal infections without bacteremia, an initial dose of 500,000 units followed by 100,000 units every 3 hours is recommended. Other penicillin-susceptible infections not involving bacteremia may be treated with similar doses, increased when necessary to 500,000 units every three hours for more severe infections. For acute gonorrhea, the oral dose is 100,000 units every 3 hours, six times daily for 1 or 2 days, or 500,000 units every 6 hours for three doses. In chronic gonorrhea with complications, a dosage of 500,000 units every four hours should be given. For prophylaxis in tonsillectomy, tooth extraction and other operative procedures in which secondary



infection may occur, the recommended oral dosage is 100,000 units every 3 hours or 250,000 to 500,000 units every 4 or 5 hours given for 1 day prior to surgery and 3 to 4 days postoperatively. The value of oral prophylaxis in rheumatic fever complicated by nasopharyngeal hemolytic streptococcic infections or for exposure to gonorrhea is not yet established. Oral therapy should not be used for meningitis, endocarditis, actinomycosis and syphilis. Whenever the response to oral medication in other infections is inadequate, the drug should be given parenterally.

### *Penicillin for Injection for Prompt Action*

**Dosage.**—The calcium, potassium or sodium salts of penicillin G and the potassium salt of penicillin O may be dissolved in sterile, pyrogen-free distilled water, isotonic solution of sodium chloride or 5 per cent dextrose solution in concentrations of 10,000 to 100,000 units per cubic centimeter. Injections may be made subcutaneously, intramuscularly or intravenously. The last route is used only for continuous infusion of concentrations of 25 to 50 units per cubic centimeter at the rate of 5,000 to 10,000 units per hour. Owing to the rapid excretion of the aqueous solutions of penicillin, injections must be repeated every 3 or 4 hours in order to maintain therapeutic blood levels.

In severe infections, continuous intravenous infusion of a solution containing 25 to 50 units per cubic centimeter should be administered at a uniform rate of 5,000 to 10,000 units per hour. In the penicillin-susceptible infections, with or without bacteremia, the average dosage is 300,000 to 600,000 units per 24-hour period; in chronic pyogenic infections, as an adjunct to surgical treatment, the dosage should be 50,000 to 100,000 units every 6 hours; in acute gonorrhea, 25,000 units may be given to hospitalized patients every 3 hours.

In meningitis, endocarditis and infections complicated by abscess formation or involving serous cavities, parenteral administration should be continued until blood cultures become negative or the acute condition is controlled. Consideration may then be given to the use of other modes of administering penicillin. In the prophylaxis of subacute bacterial endocarditis a minimum of 600,000 units daily should be employed. In the treatment of meningitis, doses not to exceed 10,000 to 20,000 units in concentrations of 1,000 units per cubic centimeter are also administered by intrathecal or intravenous injection once or twice daily, because penicillin from the blood stream does not appreciably penetrate the subarachnoid space. Since penicillin is toxic to the central nervous system, its injection into the subarachnoid space should be restricted to the concentration and amounts indicated above.

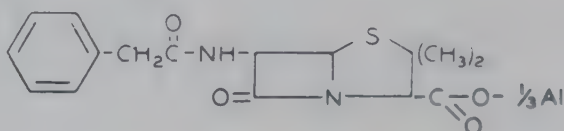
Large single doses of 250,000 units or more of aqueous crystalline penicillin administered intramuscularly once every 12 hours are adequate in uncomplicated pneumococcic pneumonia, but the shorter dosage interval is preferred when less susceptible infections are treated.

### *Penicillin for Injection for Prolonged Action*

Blood levels of penicillin G may be prolonged beyond the 3-hour or 4-hour period by various means. Vehicles which delay absorption, such as a mixture of a vegetable oil and 2 per cent aluminum monostearate, allow penicillin to be slowly absorbed from an intramuscular "depot." Various insoluble salts or esters of penicillin G such as procaine in aqueous suspension, vegetable oil or oil and 2 per cent aluminum monostearate are now chiefly used for this purpose. Excretion may be delayed by the simultaneous administration of renal blocking agents such as *p*-aminohippuric acid or probenecid.

**Dosage.**—Procaine penicillin G in oil may be used in most conditions for which aqueous penicillin solutions are suitable, and are particularly adaptable to the treatment of ambulatory patients or patients who are treated in their homes. A single dose of 300,000 units once every 24 hours usually suffices for ordinary infections due to penicillin-susceptible organisms. Severe fulminating infections, including bacterial endocarditis, should be treated with doses of 600,000 units given once or twice daily.

**ALUMINUM PENICILLIN.**—Aluminum penicillin is the trivalent aluminum salt of an antibiotic substance or substances produced by growth of the molds *Penicillium notatum* or *Penicillium chrysogenum*. The structural formula of aluminum penicillin G may be represented as follows:



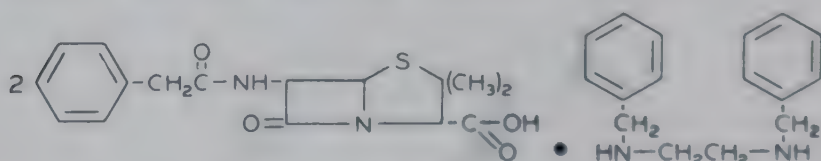
**Actions, Uses and Dosage.**—See the general statement on penicillin under Penicillin for Oral or Sublingual Administration.

HYNSON, WESTCOTT & DUNNING, INC.

Tablets Aluminum Penicillin: 50,000 units, with sodium benzoate 0.3 Gm.

U. S. patent 2,530,372.

**BENZATHINE PENICILLIN G.**—Bicillin (WYETH).—*N,N'*-dibenzylethylenediamine dipenicillin G. The structural formula of benzathine penicillin G may be represented as follows:



**Actions and Uses.**—Benzathine penicillin G is a complex salt of



penicillin. It has relatively low solubility in water and exhibits somewhat more prolonged action than more soluble salts of the drug and provides comparable blood levels. Its effective absorption from the gastro-intestinal tract is not affected appreciably by food intake; the use of added acid buffers is not required for oral administration. As with other orally administered compounds, it must be dissolved prior to intestinal absorption, but because of the limited solubility of benzathine penicillin G in the stomach, it is not highly susceptible to destruction by gastric juices. It is tasteless and is stable in aqueous suspension for 24 months at ordinary room temperatures. Orally, it produces effective blood levels when administered in adequate doses at 6-hour to 8-hour intervals. By the intramuscular route, a single injection produces an effective blood level for 1 to 4 weeks or longer, depending on the size of the dose.

Benzathine penicillin G is indicated for the prevention or treatment of infections susceptible to therapy with penicillin and, in general, it shares the same indications as other compounds of penicillin G. Because of the infrequency of injection required, parenteral administration is particularly useful for the prevention and treatment of secondary infections following tonsillectomy and tooth extraction for patients with a history of rheumatic fever, in rheumatic heart disease, and whenever prolonged penicillin protection is indicated.

Following oral administration loose stools have been observed in some patients, but in most cases no other signs of toxicity have been reported. Hypersensitivity reactions to this penicillin compound have been reported infrequently.

**Dosage.**—Benzathine penicillin G is administered orally either as a liquid suspension or as tablets and parenterally by intramuscular injection as an aqueous suspension.

Orally, a dose of 200,000 units or more every 6 to 8 hours, prescribed in liquid or tablet form, is usually adequate for mild infections. An oral dose of 200,000 units usually provides adequate blood levels for as long as 8 hours. Oral doses of 200,000 to 300,000 units every 6 to 8 hours may be necessary to maintain the blood serum concentration above 0.1 unit per cubic centimeter. The dosage for children may be calculated on the basis of 3,000 units per pound (about 6,600 units per kilogram) of body weight, administered every 8 hours. In the acute phase of pneumococcic infections (except meningitis) or in streptococcic pneumonia, an initial oral dose of 600,000 units of a potassium penicillin G preparation may be supplemented by the oral administration of 200,000 to 300,000 units every 6 to 8 hours, until temperature has remained normal for at least 48 hours. Intramuscular injection of 600,000 units can be used to initiate therapy of pneumococcic and nonhemolytic streptococcic infections without bacteremia, which may be followed by oral administration of 300,000 units every 8 hours. If bacteremia is present, the oral dose should be increased to 600,000 units or parenteral therapy should be substituted. An injection of 600,000 units every other day should be used in severe infections. In hemolytic streptococcic infections without bacteremia, 200,000 to 300,000 units orally every 6 to 8 hours for at least 7 days is recom-



mended; with bacteremia, an initial injection of 600,000 units should be given, supplemented by oral doses of 200,000 units every 8 hours. In staphylococcic infections without bacteremia, an oral dose of 300,000 units every 6 to 8 hours may be tried, but if ineffective, parenteral therapy should be substituted. When any complication or bacteremia is present in staphylococcic infections, parenteral therapy only should be used. Susceptible staphylococcic infections may be treated with a dose of 1.2 million units, repeated in 48 to 72 hours if required.

Intramuscular injection of a single dose of 600,000 units is recommended as a preventive measure 1 day prior to tonsillectomy, tooth extraction or other minor surgical procedures in patients with a history of rheumatic fever and rheumatic or congenital heart disease. In the prevention of recurrent rheumatic fever, injection of 600,000 units every 2 weeks or 1.2 million units every 4 weeks is recommended. This dosage eliminates the streptococcic carrier state in most persons. In acute beta hemolytic streptococcic infections, a single intramuscular dose of 600,000 units is usually sufficient. In acute gonorrheal urethritis, a single dose of 300,000 units intramuscularly is adequate to effect a cure in most cases. When gonorrheal urethritis is complicated with a suspected primary lesion of syphilis, it is advisable to treat the patient with either sulfonamides or with streptomycin rather than with penicillin until the diagnosis of syphilis can be verified or excluded by repeated dark-field examinations and serologic examinations of the blood repeated at monthly intervals for 3 months. In gonorrheal complications, repeated injections are rarely, if ever, necessary. In gonorrhea complicated by suspected primary syphilis, an injection of 1.2 million units may be expected to eradicate or abort syphilitic infection.

#### WYETH LABORATORIES, INC.

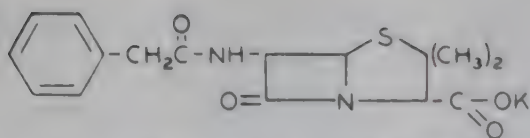
**Suspension Bicillin (Oral):** 60 cc. bottles. A flavored suspension containing 60,000 units of benzathine penicillin G in each cubic centimeter. Buffered with 0.5 per cent sodium citrate and preserved with 0.12 per cent methylparaben, 0.014 per cent propylparaben and 0.625 per cent sodium benzoate.

**Aqueous Suspension Bicillin (Injection):** 1 cc. Tubex cartridges. A suspension containing 600,000 units of benzathine penicillin G in each cubic centimeter. Buffered with 0.5 per cent sodium citrate and preserved with 0.09 per cent methylparaben and 0.01 per cent propylparaben.

10 cc. vials. A suspension containing 300,000 units of benzathine penicillin G in each cubic centimeter. Buffered with 1 per cent sodium citrate and preserved with 0.12 per cent methylparaben and 0.014 per cent propylparaben.

**Tablets Bicillin:** 100,000 and 200,000 units.

**POTASSIUM PENICILLIN G-U.S.P.**—Potassium Benzylpenicillin—"Penicillin G Potassium contain not less than 85 per cent of  $C_{16}H_{17}KN_2O_4S$ ." U.S.P. The structural formula of potassium penicillin G may be represented as follows:



**Actions and Uses.**—Penicillin G is chiefly effective against gram-positive bacteria, particularly against streptococci, pneumococci and clostridial infections, but also against gram-negative gonococci and meningococci infections. Because the incidence of infections caused by penicillinase-producing strains of staphylococci has increased greatly in recent years, staphylococcal infections have become so resistant to penicillin therapy that it is questionable whether this is the antibiotic of choice for the treatment of these infections. Penicillin G is effective in bacterial endocarditis due to susceptible organisms and against anthrax infection. It has been found very useful in the treatment of syphilis, leptospirosis, Vincent's infection and actinomycosis. It has not been demonstrated that penicillin G alone is of therapeutic value in the treatment of clinical diphtheria, and it should never be used for this purpose. However, the convalescent carrier state may be shortened by the concomitant use of adequate amounts of antitoxin and at least 240,000 units of penicillin G per day for not less than 12 days during the active clinical phase of diphtheria. Penicillin G is of little value in mixed infections in which the predominating organism is gram-negative; it is not effective against gram-negative bacillary infections, viral infections, most fungous infections, non-specific inflammatory conditions, tuberculosis, amebiasis, malaria and neoplastic diseases.

While penicillin G does not produce organic injury, it has considerable power of sensitization. Reactions of sensitivity, varying from a mild erythema or a few hives to severe serum sickness, dermatitis exfoliativa and even death from anaphylactic shock, have been reported. Topical application of penicillin G is most likely to produce sensitization and it should not be used in this way. The use of penicillin G by inhalation and as troches and lozenges has brought increased evidence of direct toxic effect on the tissues of the oropharynx. This results from irritation produced by the penicillin. *It must always be kept in mind that penicillin G may produce serious toxic reaction.*

**Dosage.**—See the general statement on penicillin under Penicillin for Inhalation, Penicillin for Oral or Sublingual Administration and Penicillin for Injection for Prompt Action.

#### ABBOTT LABORATORIES

**Potassium Penicillin G:** 100,000, 200,000, 500,000, 1,000,000 and 5,000,000 unit vials.

**Dulcet Tablets Potassium Penicillin G (Buffered):** 50,000 and 100,000 units. Buffered with 0.25 Gm. of calcium carbonate.

U. S. trademark 500,527 (Dulcet).

**Tablets Potassium Penicillin G (Buffered):** 50,000, 100,000, 200,000, 250,000 and 500,000 units. Buffered with calcium carbonate.



**Powdered Potassium Penicillin G:** 100,000 units in sifter cartridges for use in Aerohalor.

U. S. trademark 529,568 (Aerohalor Cartridge).

**Soluble Tablets Potassium Penicillin G:** 50,000, 100,000 and 250,000 units.

**COMMERCIAL SOLVENTS CORPORATION**

**Potassium Penicillin G:** 200,000 and 500,000 units in 20 cc. vials and 1,000,000 units in 50 cc. vials.

**Soltabs Potassium Penicillin G:** 50,000 and 100,000 units.

U. S. trademark 501,394 (Soltabs).

**Tablets Potassium Penicillin G (Buffered):** 50,000 and 100,000 units. Buffered with glycerides and sodium salts of fatty acids.

**R. E. DWIGHT & COMPANY**

**Potassium Penicillin G:** 100,000, 200,000, 500,000 and 1,000,000 unit vials.

**THE EVRON COMPANY, INC.**

**Soluble Tablets Potassium Penicillin G:** 50,000, 100,000, 200,000 and 250,000 units.

**Tablets Potassium Penicillin G (Buffered):** 50,000, 100,000, 200,000 and 250,000 units. Buffered with calcium carbonate.

**LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY**

**Potassium Penicillin G (Buffered):** 100,000, 200,000, 500,000, 1,000,000, 2,000,000 and 5,000,000 unit vials. Buffered with 4.5 per cent sodium citrate.

**ELI LILLY & COMPANY**

**Potassium Penicillin G:** 100,000, 200,000 and 500,000 units in 5 cc. ampuls and 1,000,000 units in 10 cc. vials.

**Tablets Potassium Penicillin G (Buffered):** 50,000, 100,000, 200,000, 250,000, 500,000 and 1,000,000 units. Buffered with calcium carbonate.

**PARKE, DAVIS & COMPANY**

**Potassium Penicillin G:** Vials of 100,000, 200,000, 500,000 and 1,000,000 units.

**Tablets Potassium Penicillin G (Buffered):** 50,000 and 100,000 units. Buffered with 0.25 Gm. of calcium carbonate.

**PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.**

**Potassium Penicillin G:** 500,000, 1,000,000, 2,000,000 and 5,000,000 unit vials.

**Soluble Tablets Potassium Penicillin G:** 50,000 and 100,000 units.



**Tablets Potassium Penicillin G (Buffered):** 50,000, 100,000, 250,000 and 500,000 units. Buffered with calcium carbonate.

**PREMO PHARMACEUTICAL LABORATORIES, INC.**

**Potassium Penicillin G:** 500,000 units in 5 cc. vials and 1,000,000 units in 20 cc. vials.

**Soluble Nebutabs Potassium Penicillin G:** 50,000, 100,000, 200,000 and 250,000 units.

**Tablets Potassium Penicillin G (Buffered):** 50,000, 100,000, 200,000, 250,000, 500,000 and 1,000,000 units. Buffered with calcium carbonate.

**REXALL DRUG COMPANY**

**Flavored Tablets Potassium Penicillin G (Buffered):** 50,000 and 100,000 units. Buffered with calcium carbonate.

**SCHENLEY LABORATORIES, INC.**

**Potassium Penicillin G:** 100,000, 200,000 and 500,000 units in 20 cc. vials. 1,000,000 and 2,000,000 units in 50 cc. vials.

**Soluble Tablets Potassium Penicillin G:** 50,000 and 100,000 units.

**E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION**

**Potassium Penicillin G (Buffered):** 100,000, 200,000, 500,000, 1,000,000 and 5,000,000 unit vials. Buffered with sodium citrate.

**Foil-Tabs Potassium Penicillin G (Buffered):** 50,000, 100,000 and 250,000 units. Buffered with 0.34 Gm. of calcium carbonate.

**Soluble Foil-Tabs Potassium Penicillin G:** 50,000 and 100,000 units.

**THE UPJOHN COMPANY**

**Potassium Penicillin G:** 25 cc. vials. 100,000, 200,000 and 500,000 units in each cubic centimeter.

50 cc. vials. 1,000,000 units in each cubic centimeter.

100,000 units in single combination packages with 20 cc. vials of sterile isotonic sodium chloride solution.

**Tablets Potassium Penicillin G (Buffered):** 50,000, 100,000 and 250,000 units. Buffered with 0.25 Gm. calcium carbonate.

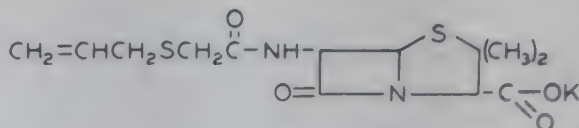
**WINTHROP-STEARNs, INC.**

**Potassium Penicillin G:** 100,000, 200,000, 500,000, 1,000,000 and 2,000,000 unit vials.

**POTASSIUM PENICILLIN O.—Cer-O-Cillin Potassium (UPJOHN).** Penicillin O is allylmercaptomethyl penicillin, produced biosynthetically by growing the mold in a medium containing allylmercaptoacetic acid.

Penicillin O is assayed in terms of the International Unit defined as the specific penicillin activity contained in 0.6 mcg. of penicillin

standard. It is stable in dry form at room temperature for a minimum of 3 years and requires no refrigeration. Solutions may be kept for 3 days under refrigeration without significant loss of potency. The structural formula of potassium penicillin O may be represented as follows:



**Actions and Uses.**—Potassium penicillin O has a spectrum of antibacterial activity similar to that of the soluble salts of penicillin G (see the general statement on penicillin). In experimental animals, penicillin O is found to be less toxic than penicillin G. Absorption and excretion curves of human beings are approximately the same for the two penicillins. Clinically penicillin O has been demonstrated to be as effective as penicillin G and to be less likely to cause sensitivity or allergic reactions. It is particularly useful as a substitute in the treatment of patients sensitive to penicillin G. Physicians should be alert to the development of drug resistant strains. In such instances, therapy should be abandoned in favor of other anti-infective agents.

Allergic reactions to penicillin O have been observed in less than 1 per cent of patients who have no history of previous allergic reactions to penicillin G. Approximately 90 per cent of patients sensitive to penicillin G tolerate therapeutic doses of penicillin O without the development of allergic phenomena. Some patients may lose their sensitivity to penicillin G during a short course of therapy with penicillin O. If reactions occur which cannot be controlled and they are more serious than the condition under treatment, the drug should be discontinued. When administered orally, penicillin O may produce an onionlike odor of the breath which subsides shortly after the drug is discontinued.

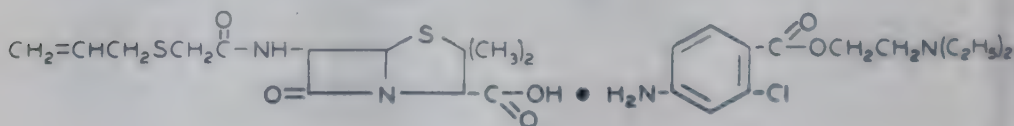
**Dosage.**—See the general statement on penicillin under Penicillin for Oral or Sublingual Administration and Penicillin for Injection for Prompt Action.

#### THE UPJOHN COMPANY

**Cer-O-Cillin Potassium:** 200,000 unit vials.

**Tablets Cer-O-Cillin Potassium (Buffered):** 100,000 units. Buffered with 0.25 Gm. calcium carbonate.

**CHLOROPROCAINE PENICILLIN O.**—Depo-Cer-O-Cillin Chloroprocaine (UPJOHN).—A crystalline salt of 2-chloroprocaine and penicillin O. The structural formula of chloroprocaine penicillin O may be represented as follows:





**Actions and Uses.**—Chloroprocaine penicillin O, a water-insoluble salt of penicillin O, has the same spectrum of anti-bacterial activity as other salts of penicillin O and penicillin G. (See the monographs on potassium penicillin G and potassium penicillin O.)

The intramuscular injection of chloroprocaine penicillin O, as a suspension dispersed in water, results in the formation of a depot of penicillin O, similar to that produced by corresponding preparations of procaine penicillin G. The levels of antibiotic in the blood produced by intramuscular injections of an aqueous suspension of chloroprocaine penicillin O are approximately equal to those obtained by a similar injection of an aqueous suspension of procaine penicillin G. With aqueous chloroprocaine penicillin O, the levels of the antibiotic in the blood usually persist for about 24 hours, as compared with 12 to 18 hours with aqueous procaine penicillin G.

As with soluble salts of penicillin O, the majority of patients sensitive to salts of penicillin G will tolerate chloroprocaine penicillin O without allergic reactions; however, some patients may be sensitive to both penicillin G and penicillin O. In such patients, another antibiotic should be used.

**Dosage.**—Chloroprocaine penicillin O is administered intramuscularly as an aqueous suspension containing 300,000 units per cubic centimeter. In acute staphylococcic, streptococcic and pneumococcic infections, the minimum dosage is 300,000 units injected once daily and continued until the temperature has returned to normal for at least 48 hours and evidence is present that the infection is disappearing. When these infections are severe, 600,000 units every 12 hours may be employed or replaced by injections of a solution of potassium penicillin O at shorter intervals. In acute gonorrhea, a single injection of 300,000 units is usually sufficient to effect a cure, but patients who fail to respond should be re-treated until a cure has been achieved. In chronic gonorrhea accompanied by complications, higher doses and more prolonged therapy may be required. In the treatment of gonorrhea, the possible masking effect of penicillin on the early signs of syphilis should be kept in mind; appropriate tests should be instituted to confirm or exclude the presence of that disease.

Aqueous suspensions may be kept at room temperature for 3 weeks without a significant loss of potency and without caking. If refrigerated, the suspension should be warmed gradually prior to injection and shaken vigorously to make certain that all of the penicillin is in suspension. Excessive heating should be avoided to prevent destruction of the physical or antibacterial properties of the suspension.

#### THE UPJOHN COMPANY

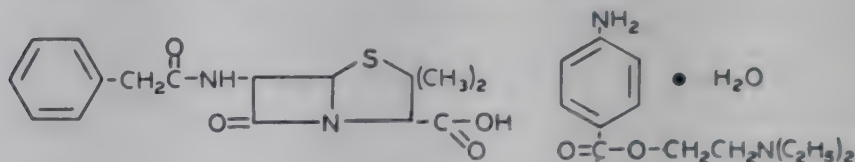
**Depo-Cer-O-Cillin Chloroprocaine:** 1,500,000 unit vials of chloroprocaine penicillin O.

U. S. patent 2,647,894. U. S. trademarks 515,760 and 554,422.

**PROCAINE PENICILLIN G-U.S.P.**—"Penicillin G Procaine is the



procaine salt of penicillin G." *U.S.P.* The structural formula for procaine penicillin G may be represented as follows:



**Actions and Uses.**—See the general statement on penicillin.

**Dosage.**—See the general statement on penicillin under Penicillin for Injection for Prolonged Action.

#### ABBOTT LABORATORIES

**Aqueous Suspension Procaine Penicillin G (Buffered):** 1 cc. cartridges with disposable cartridge syringe, 1 cc. and 10 cc. vials; 300,000 units in each cubic centimeter. Preserved with 0.135 per cent methylparaben and 0.015 per cent propylparaben. Buffered with sodium citrate and citric acid.

**Procaine Penicillin G for Aqueous Injection:** 300,000, 1,500,000 and 3,000,000 unit vials.

**Procaine Penicillin G in Oil:** 1 cc. cartridge with disposable syringe and 10 cc. vials. 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

**Rapid/Repository Penicillin Aqueous:** Buffered Potassium/Procaine Penicillin G: 1 dose (1 cc.), 5 dose (5 cc.) and 10 dose (10 cc.) vials. 100,000 units/300,000 units in each cubic centimeter. The one-dose size is packaged separately or in combination with 1 cc. ampul of water for injection as diluent.

#### BIO-RAMO DRUG COMPANY, INC.

**Aqueous Suspension Procaine Penicillin G:** 5 cc. and 10 cc. vials. A suspension containing 300,000 units of procaine penicillin G in each cubic centimeter. Preserved with 0.015 per cent butyl *p*-hydroxybenzoate. Buffered with 14 mg. of sodium citrate.

**Procaine Penicillin G in Oil:** 1 cc. and 10 cc. vials. 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

**Procaine Penicillin G in Oil:** 10 cc. vials. 300,000 units in each cubic centimeter of peanut oil with 2 per cent aluminum monostearate.

#### COMMERCIAL SOLVENTS CORPORATION

**Procaine Penicillin G (Micronized) in Oil:** 10 cc. vials. 300,000 units in each cubic centimeter in 2 per cent hydrogenated peanut oil with 2 per cent aluminum monostearate.

#### R. E. DWIGHT AND COMPANY

**Aqueous Suspension Procaine Penicillin G with Procaine Hydro-**

**chloride 2%:** 10 cc. vials. A suspension containing 300,000 units of procaine penicillin G and 20 mg. of procaine hydrochloride in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

**Procaine Penicillin G in Oil:** 10 cc. vials. 300,000 units in each cubic centimeter of peanut oil with 2 per cent (W/V) aluminum monostearate.

#### IRWIN, NEISLER & COMPANY

**Aqueous Suspension Procaine Penicillin G:** 10 cc. vials. A suspension containing 300,000 units of procaine penicillin G in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

**Procaine Penicillin G in Oil:** 10 cc. vials. A suspension in sesame oil containing 300,000 units of procaine penicillin G in each cubic centimeter with 2 per cent aluminum monostearate.

#### THE WM. S. MERRELL COMPANY

**Procaine Penicillin G in Oil:** 10 cc. vials. 300,000 units in each cubic centimeter of sesame oil.

#### PARKE, DAVIS & COMPANY

**Procaine Penicillin G in Oil:** 1 cc. disposable syringes and 10 cc. vials. 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

#### PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

**Procaine Penicillin G (Micronized) in Oil:** 10 cc. vials. A suspension containing 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

**Aqueous Suspension Procaine Penicillin G with Procaine Hydrochloride 2%:** 1 cc. Steraject cartridges. A suspension containing 600,000 units of procaine penicillin G in each cubic centimeter. Preserved with 0.12 per cent methylparaben and 0.013 per cent propylparaben. Buffered with sodium citrate.

**Procaine Penicillin G for Aqueous Injection:** Vials of 3,000,000 units. Buffered with 3.8 per cent sodium citrate.

#### PREMO PHARMACEUTICAL LABORATORIES, INC.

**Procaine Penicillin G for Aqueous Injection:** Vials of 300,000 and 3,000,000 units.

**Procaine Penicillin G (Micronized) in Oil:** 10 cc. vials. 300,000 units per cubic centimeter of sesame oil with 2 per cent (W/V) aluminum monostearate.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Procaine Penicillin G for Aqueous Injection:** 300,000, 1,500,000 and 3,000,000 unit vials. Buffered with sodium citrate.

**Procaine Penicillin G in Oil:** 10 cc. vials. 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

**E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION**

**Procaine Penicillin G (Micronized) in Oil:** 10 cc. vials. 300,000 units in each cubic centimeter of sesame oil with 2 per cent aluminum monostearate.

**STRONG COBB & COMPANY, INC.**

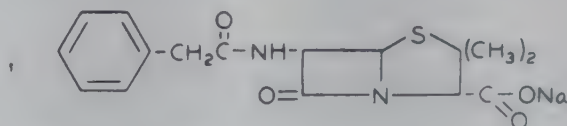
**Aqueous Suspension Procaine Penicillin G:** 1 cc. Ampins. 300,000 units in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

**THE UPJOHN COMPANY**

**Depo-Procaine Penicillin G in Oil:** 1 cc. cartridges packaged with disposable cartridge syringe and 10 cc. vials. A suspension in peanut oil containing 300,000 units of crystalline procaine penicillin G with 2 per cent aluminum monostearate.

Licensed under U. S. patent 2,507,193.

**SODIUM PENICILLIN G-U.S.P.**—Sodium Benzylpenicillin.—“Penicillin G Sodium contains not less than 85 per cent of  $C_{16}H_{17}NaO_4S$ .” *U.S.P.* The structural formula of sodium penicillin G may be represented as follows:



**Actions and Uses.**—See the monograph on potassium penicillin G.

**Dosage.**—See the general statement on penicillin under Penicillin for Inhalation, Penicillin for Oral or Sublingual Administration, and Penicillin for Injection for Prompt Action.

**BIO-RAMO DRUG COMPANY, INC.**

**Sodium Penicillin:** 200,000 and 500,000 unit vials.

**Sodium Penicillin G (Buffered):** 200,000, 500,000 and 1,000,000 unit vials.

**Tablets Sodium Penicillin G (Buffered):** 50,000 and 100,000 units Buffered with sodium benzoate.

**R. E. DWIGHT & COMPANY**

**Sodium Penicillin G:** 100,000, 200,000, 500,000 and 1,000,000 unit vials.

**THE WM. S. MERRELL COMPANY**

**Sodium Penicillin:** 100,000, 200,000, 500,000 and 1,000,000 unit vials.



SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

Sodium Penicillin G: 100,000, 200,000 and 500,000 units in 5 cc. vials and 1,000,000 units in 20 cc. vials.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

Powdered Sodium Penicillin G: 100,000 units in Dispolator vials.

## Polymyxin

Polymyxin is the generic term employed to designate a series of related antibiotics derived from various strains of the spore-forming soil bacterium, *Bacillus polymyxa* (*B. aerosporus* Greer). The various polymyxins which have been isolated are differentiated by affixing letters of the alphabet which do not necessarily signify the order of isolation. Polymyxin B is the least toxic of those adequately studied. Chemically, the polymyxins are basic polypeptides. Polymyxin B contains leucine, threonine, phenylalanine,  $\alpha,\gamma$ -diaminobutyric acid and a fatty acid of empirical formula,  $C_9H_{18}O_2$ , and has a molecular weight of about 1,000. It is stable as the acid salt, polymyxin B sulfate, in the dry state; in solution it is stable for extended periods. Alkaline solutions are less stable. The antibiotic is highly effective in vitro against many gram-negative micro-organisms. See the monograph on polymyxin B sulfate.

**POLYMYXIN B SULFATE.**—Aerosporin Sulfate (BURROUGHS WELLCOME).—A basic polypeptide containing leucine, threonine, phenylalanine,  $\alpha,\gamma$ -diaminobutyric acid and a fatty acid of unknown structure (empirical formula,  $C_9H_{18}O_2$ ).

**Physical Properties.**—Polymyxin B sulfate is a white to cream-colored irregular scalelike material, which has no definite melting point, but decomposes at about 230°. It is soluble in water and isotonic sodium chloride solution. A 2 per cent solution has a pH of about 5.7.

**Actions and Uses.**—Polymyxin B sulfate, an antibiotic derived from an isolated strain of *Bacillus polymyxa*, is bactericidal in vitro for most gram-negative micro-organisms. *Escherichia coli*, *Shigella*, *Pseudomonas aeruginosa* (*B. pyocyaneus*), *Aerobacter aerogenes*, *Klebsiella pneumoniae* and *Hemophilus influenzae* are sensitive to polymyxin B sulfate concentrates of 0.05 to 2 mcg. per cubic centimeter. *Proteus vulgaris* (*B. proteus*) is usually more resistant. Most strains of *P. aeruginosa* are highly sensitive. Clinical observations indicate that the development of bacterial resistance is unlikely.

Polymyxin B sulfate is effective clinically by intramuscular injection (and intrathecally, when indicated) for the treatment of pseudomonal (pyocyaneal) bacteremia, meningitis and urinary tract infection and for the treatment of meningitis caused by other gram-negative bacilli such as *Aerobacter aerogenes*, *E. coli*, *K. pneumoniae*, and *H. influenzae* when these are more sensitive to polymyxin B than to other effective antibiotics. Since the antibiotic

does not readily pass into the spinal fluid when given intramuscularly, the drug should be given intrathecally as well as intramuscularly for the treatment of susceptible meningeal infections. The intrathecal doses required do not produce systemic toxic effects and the drug is considered relatively nonirritating to the meninges. Intrathecal injections should be made with the care that is essential in the performance of repeated spinal punctures.

Polymyxin B sulfate, when given parenterally, may produce neurotoxic and/or nephrotoxic effects, but it has a low degree of toxicity when used in doses below 3 mg. per kilogram of body weight per day. Neurologic disturbances are usually subjective and include dizziness, mild weakness and paresthesias of the mouth, face, and, less frequently, of the extremities. These are not usually considered sufficiently serious to warrant discontinuance of therapy. Nephrotoxic effects, with damage to the kidney tubular epithelium, are manifested by albuminuria and nitrogen retention. The danger of renal damage is minimal when the drug is administered within the recommended dosage range. Other toxic effects include occasional drug fever and pain at the site of injection which can be lessened by employing 1 per cent procaine hydrochloride solution in the diluent. The possible danger of renal damage makes it desirable to limit the parenteral use of the drug to patients who are under close observation where there is access to adequate laboratory facilities. Renal dysfunction and nitrogen retention do not contraindicate injection of the drug when it is specifically indicated unless such use is found to aggravate preexisting renal damage.

Polymyxin B sulfate also may be useful orally in the nonsystemic treatment of certain intestinal infections such as *Shigella* or *Pseudomonas enteritis*, when present as a pathogen. It is too poorly absorbed orally to warrant use by this route in the treatment of systemic infections. Toxic manifestations have not been observed with oral use of the drug.

Polymyxin B sulfate is also useful by topical application for the treatment of local infections caused by susceptible gram-negative bacilli, especially *Pseudomonas aeruginosa*. It may be employed locally also to prevent contamination by gram-negative organisms of wounds or burns.

An ophthalmic ointment containing 20,000 units per gram also may be employed for the treatment and preoperative prophylaxis of eye infections, but it should not be used alone in ocular infections which involve deep structures of the eye or in those infections which may become systemic.

**Dosage.**—Intramuscularly, the average daily dosage extends from 1.5 mg. (15,000 units) to 2.5 mg. (25,000 units) per kilogram of body weight. The total daily dosage should not exceed 2.5 mg. per kilogram and, in any case, not more than 0.2 Gm. (2,000,000 units). The drug is usually administered in three divided doses at 6-hour to 8-hour intervals. Such doses provide therapeutic blood serum levels of 1 to 8 mcg. per cubic centimeter. The peak level is reached within 30 minutes to 2 hours after injection; one-half the peak level is present after 6 hours, with detectable levels up to 12



hours' duration. In patients with impaired renal function and nitrogen retention, a dosage of 20 mg. every 8 hours maintains serum levels at 2.5 mcg. per cubic centimeter. A solution for intramuscular use is prepared by dissolving 50 mg. in water for injection-U.S.P., sterile isotonic sodium chloride solution or 0.5 cc. of 1 per cent sterile procaine hydrochloride solution. If procaine is used, the usual precaution should be observed.

Intrathecally, the following doses are suggested: Children under 2 years of age, 2 mg. daily for 3 or 4 days, then 2.5 mg. every other day; children over 2 years and adults, 5 mg. daily for 3 or 4 days, then 5 mg. every other day. A solution for intrathecal injection is prepared by adding 10 cc. of sterile isotonic sodium chloride solution to 50 mg. of the drug. Solutions prepared for intramuscular use and containing procaine should not be used for intrathecal administration.

Orally, for adults and older children, the dosage is 75 to 100 mg. four times daily; children 2 to 5 years of age, 50 to 75 mg. three times daily; children up to 2 years of age, 25 to 50 mg. three times daily. For infants and young children the tablets may be crushed and mixed with a suitable food or dissolved in water and flavored as desired.

For topical application, the drug, in sterile dry form, is dissolved in distilled water or isotonic sodium chloride solution for administration as drops, spray, wet dressing or irrigation. Concentrations of 0.1 per cent (10,000 units per cubic centimeter) to 0.25 per cent (25,000 units per cubic centimeter) are considered to be effective and nonirritating. Concentrations of 1 per cent or more may produce local irritation when applied to sensitive areas such as the eye. Neither bacterial resistance nor sensitivity reactions have been observed, but until further experience is gained, a total of not more than 2,000,000 units daily should be applied in cases of severe burns and open wounds. Solutions of the antibiotic are stable for at least six months if kept under refrigeration.

A small quantity of ophthalmic ointment is placed in the conjunctival sac, three or four times daily, for the treatment of superficial, susceptible infections; as a preoperative prophylactic, it is applied to both eyes on the day prior to surgery.

#### BURROUGHS WELLCOME & COMPANY, INC.

**Aerosporin Sulfate (*Parenteral*):** 500,000 unit vials. Each vial contains 500,000 units of polymyxin B sulfate equivalent to 50 mg. of polymyxin B standard.

**Sterile Powder Aerosporin Sulfate (*Topical*):** 200,000 unit vials. Each vial contains 200,000 units of polymyxin B sulfate equivalent to 20 mg. of polymyxin B standard.

**Tabloid Aerosporin Sulfate:** 500,000 units. Each vial contains 500,000 units of polymyxin B sulfate equivalent to 50 mg. of polymyxin B standard.

U. S. patent 2,565,057. U. S. trademark 505,252.



PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

**Ointment Polymyxin B Sulfate:** 14.2 Gm. tubes. An ointment containing 20,000 units of polymyxin B as the sulfate in each gram.

**Ophthalmic Ointment Polymyxin B Sulfate:** 3.5 Gm. tubes. An ointment containing 20,000 units of polymyxin B as the sulfate in each gram.

**Sterile Powder Polymyxin B Sulfate (*Parenteral*):** 500,000 unit vials. Each vial contains 500,000 units of polymyxin B sulfate equivalent to 50 mg. of polymyxin B standard.

**Sterile Powder Polymyxin B Sulfate (*Topical*):** 200,000 unit vials. Each vial contains 200,000 units of polymyxin B sulfate equivalent to 20 mg. of polymyxin B standard.

**Soluble Tablets Polymyxin B Sulfate:** 250,000 units of polymyxin B as the sulfate.

## Streptomycin and Dihydrostreptomycin

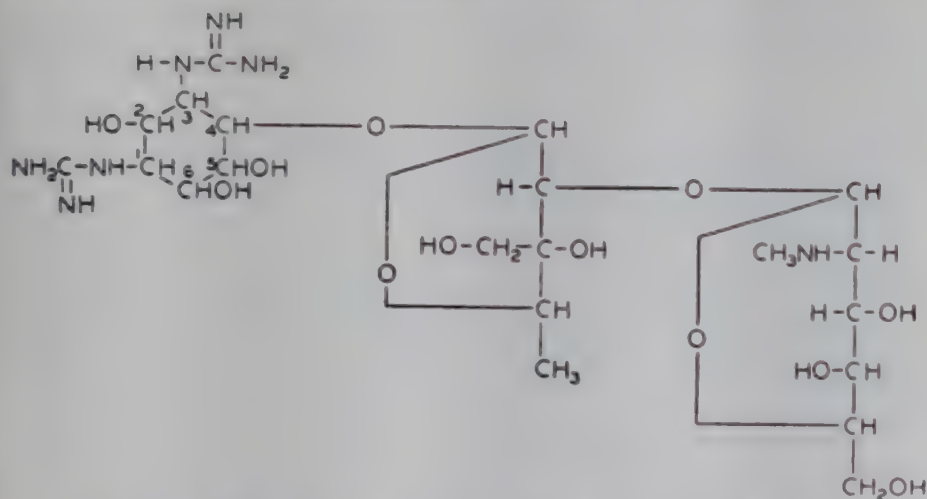
Streptomycin is a basic organic compound of moderate molecular size.

When streptomycin is administered by mouth, practically none is absorbed and the bulk of the dose is excreted in the stool. The same is true when streptomycin aerosols are inhaled. For this reason streptomycin must be administered parenterally for the treatment of systemic infections. Maximal concentrations in the blood occur at the end of intravenous injections. Following intramuscular injection, there is a gradual rise, peak levels of streptomycin being found in the blood in 1 to 2 hours. While there is some evidence that the blood concentrations of streptomycin are maintained longer after intramuscular injection, the levels may fall so rapidly that only small amounts of streptomycin are found in the blood 4 hours after intramuscular injection of a therapeutic dose. The concentration and persistence of streptomycin in the blood are related to the size of the dose injected, but are not proportional to it.

Excretion by the kidneys is greatest in the 2 hours following intramuscular or intravenous injection of streptomycin; 30 to 60 per cent may be excreted in the urine within 12 hours if renal function is normal, and the bulk is excreted within 24 hours. A small amount is excreted in the bile and eliminated in the stool. Small quantities of this antibiotic are excreted in milk, saliva, sweat and tears. When renal function is seriously impaired, the rate of excretion of streptomycin is decreased and the drug accumulates in the blood. Since streptomycin and dihydrostreptomycin have a direct toxic effect on the vestibular apparatus which in some degree is proportional to the dose, care must be taken to prevent unnecessarily high blood concentrations in patients with impaired renal function.

Streptomycin does not pass readily into red blood cells, and it apparently does not pass into the pus in abscesses. The antibiotic is distributed only in the extracellular water of the body. It diffuses so slowly into the spinal fluid that in many instances it may not be detectable, despite repeated parenteral injections. On the other hand, it has been reported to occur in easily detectable amounts in the spinal fluid of patients with frank meningitis. This antibiotic passes over slowly into pleural, synovial and pericardial effusions and, when present, concentrations are almost always considerably lower than those in the blood. Streptomycin passes easily into normal peritoneal fluid or into the exudate of a peritonitis, and it is found in ascitic fluid, generally in concentrations lower than those in the blood. Intramuscular injection produces adequate concentrations of streptomycin in the aqueous and vitreous humors. The concentrations which pass into fetal blood and amniotic fluid are about half of those in the maternal blood.

**DIHYDROSTREPTOMYCIN-U.S.P.**—"Dihydrostreptomycin is produced by the hydrogenation of streptomycin. It is usually available as the hydrochloride,  $C_{21}H_{41}N_7O_{12} \cdot 3HCl$  or as the sulfate  $(C_{21}H_{41}N_7O_{12})_2 \cdot 3H_2SO_4$ . Dihydrostreptomycin base is not available. It complies with the requirements of the Federal Food and Drug Administration." *U.S.P.* The structural formula of dihydrostreptomycin may be represented as follows:



Dosage of dihydrostreptomycin salts is expressed in terms of dihydrostreptomycin base. The salts are soluble in aqueous mediums, but are generally insoluble in organic solvents. The dried powder is stable at room temperature for 18 months; the solution shows no appreciable loss of potency for as long as one month. For injection, salts of dihydrostreptomycin may be dissolved in pyrogen-free, sterile distilled water; isotonic sodium chloride solution; or 5 per cent dextrose solution, by adding the equivalent of 250 to 500 mg. of dihydrostreptomycin base per cubic centimeter

of solvent. A solution of 1 per cent procaine hydrochloride or the equivalent of other suitable local anesthetic in distilled water may also be used as a solvent.

**Physical Properties.**—Dihydrostreptomycin (hydrochloride or sulfate) occurs as white or faintly yellow granules or as a white powder. It is nearly odorless and has a slightly bitter taste. It is not affected by air or light and does not deliquesce.

**Actions and Uses.**—See the monograph on streptomycin.

**Dosage.**—Dihydrostreptomycin is administered as the hydrochloride or sulfate in doses similar to those of streptomycin. Unlike streptomycin, dihydrostreptomycin must be injected by the intramuscular route only. *It must not be injected intravenously.* The sulfate may be given by the intrathecal route in doses not to exceed 1 mg. per pound of body weight up to 50 pounds of weight. It may be given daily or on alternate days. Intraspinal therapy is rarely indicated in any condition other than tuberculous meningitis.

Intramuscular injection of the drug may cause pain, which may be reduced by observance of the following suggestions: (a) allow 12-hour intervals between injections; (b) use only fresh solutions; (c) restrict maximum volume of injection at any one site to 2 cc.; (d) use the upper outer quadrant of the buttocks and change site for each injection; (e) insert needle deeply to avoid subcutaneous deposition and inject slowly; (f) as the diluent, use a local anesthetic with distilled water; (g) avoid concentrations whose dihydrostreptomycin base equivalent is greater than 500 mg. per cubic centimeter of solvent. Each 500 mg. equivalent of the powder contributes approximately 0.3 cc. to the volume of solution made

#### ABBOTT LABORATORIES

**Dihydrostreptomycin Sulfate:** Vials of dihydrostreptomycin sulfate powder, containing the equivalent in activity to 1 Gm. or 5 Gm. of dihydrostreptomycin base.

**Solution Dihydrostreptomycin Sulfate:** 2 cc. vial. A solution containing dihydrostreptomycin sulfate equivalent in activity to 0.5 Gm. of dihydrostreptomycin base in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol and 0.1 per cent sodium metabisulfite.

#### BIO-RAMO DRUG COMPANY, INC.

**Dihydrostreptomycin Sulfate:** Vials of dihydrostreptomycin sulfate powder, containing the equivalent in activity to 1 Gm. or 5 Gm. of dihydrostreptomycin base.

#### ELI LILLY & COMPANY

**Dihydrostreptomycin Sulfate:** 5 cc. and 20 cc. ampuls. Dihydrostreptomycin sulfate powder equivalent in activity to 1 Gm. and 5 Gm., respectively, of dihydrostreptomycin base.

**Solution Dihydrostreptomycin Sulfate:** 2 cc. ampuls and 10 cc. vials. A solution containing dihydrostreptomycin sulfate equivalent in activity to 1 Gm. and 0.5 Gm., respectively, of dihydrostrepto-



mycin base in each cubic centimeter. Preserved with 0.25 per cent phenol.

#### THE WM. S. MERRELL COMPANY

**Dihydrostreptomycin Sulfate:** 5 cc. and 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 Gm. and 5 Gm., respectively, of dihydrostreptomycin base.

PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

**Dihydrostreptomycin Sulfate:** 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 Gm. or 5 Gm. of dihydrostreptomycin base.

**Solution Dihydrostreptomycin Sulfate:** 2 cc. Steraject cartridges, 2 cc. and 10 cc. vials. A citrate buffered solution containing the equivalent of 0.5 Gm. of dihydrostreptomycin base in each cubic centimeter. Stabilized with 1 per cent sodium bisulfite and preserved with 0.25 per cent phenol.

#### PREMO PHARMACEUTICAL PRODUCTS, INC.

**Dihydrostreptomycin Sulfate:** 5 cc. and 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 Gm. and 5 Gm., respectively, of dihydrostreptomycin base.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Dihydrostreptomycin Sulfate:** 2 cc. and 10 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 Gm. and 5 Gm., respectively, of dihydrostreptomycin base.

**Solution Dihydrostreptomycin Sulfate:** 2 cc. and 10 cc. vials. A solution containing dihydrostreptomycin sulfate equivalent in activity to 1 Gm. and 5 Gm. of dihydrostreptomycin base, respectively. Buffered with 1.5 per cent sodium citrate. Preserved with 0.2 per cent sodium bisulfite.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Dihydrostreptomycin Sulfate:** 5 cc. and 20 cc. vials. Dihydrostreptomycin sulfate powder equivalent in activity to 1 Gm. and 5 Gm., respectively, of dihydrostreptomycin base.

#### THE UPJOHN COMPANY

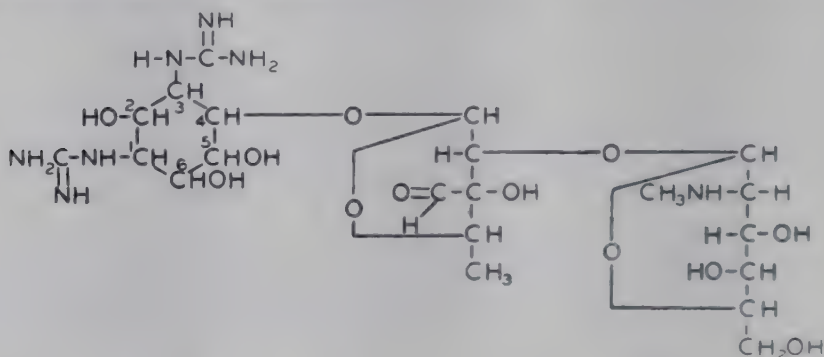
**Dihydrostreptomycin Sulfate:** 5 cc. and 20 cc. vials. Dihydrostreptomycin powder equivalent in activity to 1 Gm. and 5 Gm., respectively, of dihydrostreptomycin base.

**Solution Dihydrostreptomycin Sulfate:** 2 cc. and 10 cc. vials. A solution containing dihydrostreptomycin sulfate equivalent in activity to 0.5 Gm. of dihydrostreptomycin base in each cubic centimeter. Preserved with 0.25 per cent phenol.

**STREPTOMYCIN-U.S.P.**—"Streptomycin consists of the several antibiotic substances produced by the growth of *Streptomyces*

*griseus* (Krainsky) Waksman et Henrici (Fam. *Actinomycetaceae*), or each of the same substances produced by any other means. It is usually available as the hydrochloride,  $C_{21}H_{39}N_7O_{12} \cdot 3HCl$ ; as the hydrochloride double salt with calcium chloride,  $(C_{21}H_{39}N_7O_{12} \cdot 3HCl)_2CaCl_2$ ; as the phosphate,  $C_{21}H_{39}N_7O_{12} \cdot H_3PO_4$ ; or as the sulfate  $(C_{21}H_{39}N_7O_2)_2 \cdot 3H_2SO_4$ . It complies with the requirements of the Federal Food and Drug Administration." U.S.P. Streptomycin is marketed as a sterile powder in airtight ampuls or vials. Its potency is not less than 300 mcg. per milligram. At least two forms, designated A and B, have been isolated so far.

Streptomycin in dry form may be stored at room temperature, not exceeding  $30^\circ$ , for periods up to 2 years; however, it should be stored in the original unopened container to prevent contamination and deliquescence. Solutions of streptomycin may be stored at room temperature for 1 week without significant loss of potency. Solutions which have been acidified or alkalinized, i.e., those having a pH lower than 4 or higher than 7, are less stable. Streptomycin solutions should not be autoclaved, and only freshly prepared solutions should be used parenterally because of the potential danger of contamination. The structural formula of streptomycin may be represented as follows:



**Physical Properties.**—In salt form, streptomycin occurs as white to slightly pink or pale-brown granules or powder. It has a slightly bitter taste and is odorless, or nearly so. It is hygroscopic and may deliquesce on exposure to air. It is very soluble in water but is almost insoluble in alcohol, chloroform and ether.

**Actions and Uses.**—Streptomycin and dihydrostreptomycin have essentially the same actions and uses. Originally both of these compounds were effective against a variety of gram-negative and gram-positive pathogenic bacteria, including the tubercle bacillus. However, as time passed, and the use of these two antibiotics became widespread, the emergence of strains of pathogenic bacteria, which were resistant to the antibacterial effects of these antibiotics, was increasingly noted. As has been pointed out previously, the majority of strains of certain of the gram-negative pathogens, such as *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Aerobacter aerogenes*, now being isolated from infectious processes, are resistant to these antibiotics. The same is true for strains of *Streptococcus fecalis*. For these reasons, the use of streptomycin or dihydro-



streptomycin should be limited to the treatment of infections produced by bacteria which have been shown by laboratory tests to be susceptible to the antibacterial effects of these two antibiotics. In fact, a number of authorities in this field now recommend that streptomycin or dihydrostreptomycin be used only in the treatment of suitable cases of tuberculosis, except in those special instances of infection proved to be susceptible to these antibiotics.

Both streptomycin and dihydrostreptomycin may produce toxic effects such as drug fever, dermatitis or other allergic manifestations. The most serious toxic effects produced by either are those involving the eighth nerve. Permanent and grave damage marked by severe vertigo and/or loss of hearing may occur. Because of these possibilities, careful audiometric and vestibular function tests should be made prior to and during therapy with either streptomycin or dihydrostreptomycin. Deafness may develop within a month or so after treatment with dihydrostreptomycin has been discontinued. Persons who are frequently in contact with these antibiotics, such as pharmacists, nurses or attendants who administer them, or attendants in central supply rooms where syringes used for the administration of these antibiotics are cleaned, may develop contact dermatitis. For this reason, they should protect themselves by wearing rubber gloves, masks, and spectacles when in contact with these antibiotics.

**Dosage.**—For intramuscular injection, the powder should be dissolved in sterile, pyrogen-free distilled water or isotonic solution of sodium chloride to give a concentration of 100 to 200 mg. of streptomycin base per cubic centimeter. For subcutaneous injection, more dilute solutions are recommended. If the drug is administered by intravenous drip, 1 to 2 Gm. dissolved in a liter of isotonic solution of sodium chloride may be administered at a rate of about 25 drops per minute. For intrathecal administration, 10 to 20 mg. per cubic centimeter in isotonic sodium chloride solution should be used. For topical application, solutions containing 25 to 50 mg. per cubic centimeter may be used.

The dosage of streptomycin should be governed by the susceptibility of the organism responsible for the infection. In severe fulminating infections, doses of 2 to 4 Gm. daily may be necessary, given parenterally in divided doses every 6 hours. In less severe infections, and with highly susceptible organisms, daily doses of 1 to 2 Gm. may be sufficient. Treatment should be continued for at least 48 to 72 hours after the temperature returns to normal and all signs of infection have disappeared. As an adjunct to other forms of therapy in all types of tuberculosis except the miliary and meningeal forms, doses of 1 Gm. of streptomycin are given intramuscularly two or three times weekly in conjunction with *p*-aminosalicylic acid for a total of 120 days. In acute miliary tuberculosis and tuberculous meningitis, intramuscular doses of 2 Gm. or more daily are given. In tuberculous meningitis, the intrathecal injection of 50 mg. of streptomycin every 1 or 2 days may be used in conjunction with the intramuscular administration of streptomycin.

For inhalation therapy with an aerosol of streptomycin, the sul-



fate is dissolved in distilled water to make a solution containing the equivalent of 50 to 100 mg. of the base in each cubic centimeter. Nebulization of an amount (1 or 2 cc.) sufficient to provide inhalation of 100 mg. five or six times daily every 3 hours is recommended as an adjunct to systemic therapy in nontuberculous bronchial and pulmonary infections. It may be administered in the same solution with crystalline sodium penicillin when the latter drug is simultaneously indicated; potassium penicillin may cause turbidity or opalescence.

It is important to give sufficiently large doses to inhibit or kill the infecting organisms quickly, since the development of "fastness" to streptomycin is common and may occur rapidly. Inadequate dosage predisposes to the development of resistant strains of the organisms.

#### ABBOTT LABORATORIES

**Streptomycin Sulfate:** 20 cc. vials. Vials of streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base.

#### BIO-RAMO DRUG COMPANY, INC.

**Streptomycin Calcium Chloride Complex:** Vials of streptomycin calcium chloride complex equivalent in activity to 1 Gm. of streptomycin base.

#### THE WM. S. MERRELL COMPANY

**Streptomycin Sulfate:** 5 cc. and 20 cc. vials. Streptomycin sulfate equivalent in activity to 1 Gm. and 5 Gm. of streptomycin base, respectively.

#### PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC.

**Streptomycin Sulfate:** Bulk, for manufacturing use only.

**Streptomycin Sulfate:** 20 cc. vials. Streptomycin sulfate equivalent in activity to 1 Gm. or 5 Gm. of streptomycin base.

**Solution Streptomycin Sulfate:** 2 cc. Steraject cartridges, 2 cc. and 10 cc. vials. A citrate buffered solution containing the equivalent of 0.5 Gm. of streptomycin base in each cubic centimeter. Stabilized with 0.2 per cent sodium bisulfite and preserved with 0.25 per cent phenol.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Streptomycin Calcium Chloride Complex:** 5 cc. and 20 cc. vials. Streptomycin calcium chloride complex equivalent in activity to 1 Gm. and 5 Gm. of streptomycin base, respectively.

U. S. patent 2,446,102.

#### E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Streptomycin Sulfate:** 5 cc. and 20 cc. vials. Streptomycin sulfate equivalent in activity to 1 Gm. and 5 Gm., respectively, of streptomycin base.

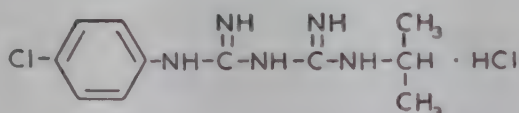
## THE UPJOHN COMPANY

**Streptomycin Sulfate:** 30 cc. vials. Streptomycin sulfate equivalent in activity to 1 Gm. of streptomycin base.

**TYROTHRIN.**—For monograph see the chapter on local anti-infectives.

## ANTIMALARIAL AGENTS

**CHLOROGUANIDE HYDROCHLORIDE-U.S.P.**—Guanatol Hydrochloride (LILLY).—1-(*p*-Chlorophenyl)-5-isopropylbiguanide hydrochloride.—“Chloroguanide Hydrochloride dried at 105° for 2 hours contains not less than 98 per cent of  $C_{11}H_{16}ClN_5 \cdot HCl$ .” U.S.P. The structural formula of chloroguanide hydrochloride may be represented as follows:



**Physical Properties.**—Chloroguanide hydrochloride occurs as colorless crystals or as a white, crystalline powder. It is odorless, has a bitter taste and melts between 248 and 250°. One gram of this drug dissolves in about 75 cc. of water and in about 30 cc. of alcohol. It is insoluble in chloroform and ether.

**Actions and Uses.**—Chloroguanide hydrochloride is useful for the prophylaxis, suppression and treatment of malignant tertian (*Plasmodium falciparum*) malaria and for the suppression and treatment of the strains of benign tertian (*Plasmodium vivax*) malaria studied so far. The drug is only partially effective in preventing attacks of vivax malaria, erythrocytic forms appearing in the blood a short time after the drug is withdrawn. Other antimalarial drugs such as chloroquine or quinacrine are preferable in the treatment of vivax malaria.

Chloroguanide hydrochloride disappears from the plasma within 48 hours after the oral administration of a single dose of 0.5 Gm. From one-half to one-third of the drug is excreted by the kidneys. The drug does not accumulate in the body when given in therapeutic doses.

No toxic effects are observed in the usual dosage regimen, but doses of 1 Gm. or more may produce vomiting, abdominal pain, and diarrhea. Excessive doses may produce transient hematuria, epithelial cells, and casts in the urine. Intramuscular injection of chloroguanide hydrochloride may result in local myonecrosis and inflammatory reactions. Large doses injected may also produce a temporary myelocytic reaction in the blood.

Different strains of plasmodia vary in their response to this as to other antimalarial agents. Therefore, the average dosage schedule indicated below is subject to modification according to the response of the individual strain.

**Dosage.**—A single dose of 0.3 Gm. weekly is effective in the sup-

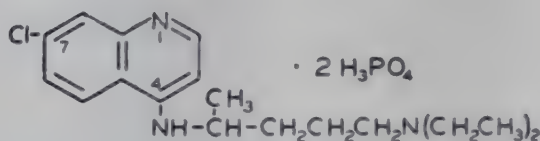
pression of falciparum and vivax malaria. For the prophylaxis of falciparum malaria, 0.1 Gm. may be given twice weekly; this dose is only partially effective against vivax malaria.

A dose of 0.1 Gm. three times daily, or 0.3 Gm. daily, for 10 days usually cures falciparum malaria. This dose is usually only partially effective against vivax malaria.

ELI LILLY & COMPANY

Tablets Guanatol Hydrochloride: 100 mg.

**CHLOROQUINE PHOSPHATE-U.S.P.**—**Aralen Phosphate** (WINTHROP-STEARNs). — 7-Chloro-4-(4-diethylamino-1-methylbutyl-amino)quinoline diphosphate. — "Chloroquine Phosphate, dried at 105° for 2 hours, contains not less than 98 per cent of  $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$ ." U.S.P. The structural formula of chloroquine phosphate may be represented as follows:



**Physical Properties.**—Chloroquine phosphate is a white, crystalline powder. It is odorless, has a bitter taste and slowly discolors on exposure to light. Its solution is acid to litmus paper, having a pH of about 4.5. It is freely soluble in water, almost insoluble in alcohol, chloroform and ether.

**Actions and Uses.**—Chloroquine phosphate has approximately three times the activity of quinacrine hydrochloride against standardized strains of *P. vivax* and *P. falciparum*.

Chloroquine phosphate is rapidly and completely absorbed by the gastro-intestinal tract. Some of it is excreted slowly in the urine. Considerable amounts are deposited in the organs and tissues, being concentrated in nucleated cells, particularly those of the liver, spleen, kidneys and lung.

Chloroquine phosphate is slowly metabolized in the body, and may be detected in body tissues for more than a week after medication is discontinued.

Chloroquine phosphate is active against the erythrocytic forms of *P. vivax* and *P. falciparum*. It does not prevent relapses in vivax malaria, nor does it prevent the establishment of vivax infection when administered as a prophylactic. It is effective as a suppressive agent in vivax malaria and for the termination of acute attacks, lengthening the interval between treatment and relapse. In falciparum malaria, chloroquine phosphate abolishes the acute attack and completely cures the infection.

Chloroquine phosphate also possesses amebacidal properties and, because of its localization in various organs, is highly effective in the treatment of extra-intestinal amebiasis. Since systemic and, especially, hepatic involvement often occur early in amebiasis, without clinical signs, some physicians consider it wise to ad-



minister a drug with systemic effect, such as chloroquine or emetine. While these drugs may give initial symptomatic relief, they should not be relied upon to effect a cure of the intestinal form of the disease, but should be supplemented by agents which reach the lower bowel in concentrations sufficient to establish a cure. These agents include certain arsenical and oxyquinoline drugs, and possibly some of the newer antibiotics.

The drug is well tolerated in therapeutic doses and does not produce cinchonism or discoloration of the skin. However, mild headache, pruritus, visual disturbances and gastro-intestinal complaints may follow therapeutic doses. Blurring of vision and difficulty in focusing are occasionally observed following prolonged administration. None of the side reactions is serious, and all are reversible.

Because of its localization in the tissues of various organs and its amebicidal effects, chloroquine phosphate is useful for the oral treatment of extra-intestinal amebiasis. It is preferable to injected emetine hydrochloride for the treatment of amebic hepatitis and abscess. It is not recommended for intestinal forms of amebiasis.

**Dosage.**—Chloroquine phosphate is usually administered orally either before or after meals.

A total of 2.5 Gm. in 3 days is sufficient to eradicate most infections with *P. falciparum*, and to terminate acute attacks of vivax malaria. An initial dose of 1 Gm. is supplemented by 0.5 Gm. after 6 or 8 hours and by 0.5 Gm. on each of the two succeeding days. Freedom from clinical attacks of vivax malaria is maintained by administration of suppressive doses of 0.5 Gm. at exactly 7-day intervals.

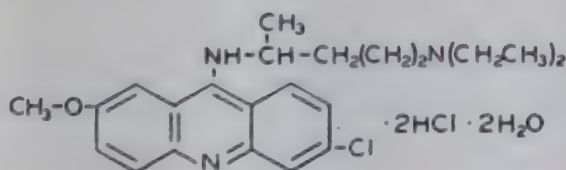
For the treatment of extra-intestinal amebiasis, 1 Gm. per day in divided doses is administered orally for 2 days, to saturate the tissues and to obtain a constant plasma concentration. Maintenance is then provided by 0.5 Gm. daily (0.25 Gm. twice daily) for 2 or 3 weeks.

WINTHROP-STEARN, INC.

Tablets Aralen Phosphate: 0.25 Gm.

U. S. patent 2,233,970.

**QUINACRINE HYDROCHLORIDE-U.S.P.** — Atabrine Hydrochloride (WINTHROP-STEARN). — 3-Chloro-7-methoxy-9-(1-methyl-4-diethylaminobutylamino)acridine dihydrochloride dihydrate. — Mepacrine Hydrochloride. — "Quinacrine Hydrochloride contains not less than 98 per cent of  $C_{23}H_{30}ClN_3O \cdot 2HCl \cdot 2H_2O$ ." U.S.P. The structural formula of quinacrine hydrochloride may be represented as follows:



**Physical Properties.**—Quinacrine hydrochloride occurs as a bright yellow, crystalline powder. It is odorless and has a bitter taste. One gram dissolves in about 30 cc. of water. It is soluble in alcohol.

**Actions and Uses.**—Quinacrine hydrochloride destroys the asexual forms (trophozoites) of the causative organism in all types of malaria and thus checks the progress of the disease. Given during the first paroxysms of a benign tertian (*Plasmodium vivax*) attack it will often decrease the severity of the second paroxysm and completely prevent the appearance of the third. In ordinary cases of benign tertian malaria and also in the more rare quartan (*P. malariae*) malaria, it produces better results than does quinine. Relapses are less frequent than with quinine and the period of treatment is shorter. Quinacrine hydrochloride is more effective than quinine in the treatment of malignant subtertian (*P. falciparum*) malaria. It is of value in the treatment of blackwater fever when quinine is contraindicated. Like quinine the drug partially destroys the sexual forms (gametocytes) of the malarial organisms and thus lessens the extent to which the patient may act as a reservoir from which mosquitoes may be infected. If taken faithfully in suppressive doses quinacrine hydrochloride lengthens the interval between relapses of malaria more effectively than quinine.

Quinacrine hydrochloride is effective in combating *Giardia lamblia* infestation, but the evidence that this organism is pathogenic for man or is the cause of diarrhea and other symptoms associated with its presence in the gastro-intestinal tract is inconclusive.

Quinacrine hydrochloride causes the urine to become very yellow on the third to fifth day, and, being of an acridine dye nature, it may cause temporary discoloration of the skin. Headache and mild gastro-intestinal symptoms occur frequently. The drug does not cause visual or aural disturbances and may therefore be preferred to quinine. The circulatory system is not disturbed by therapeutic doses of quinacrine hydrochloride. The drug is not toxic to the liver or kidneys. Some patients claim that quinacrine hydrochloride is stimulating. A few psychotic attacks, some severe, have been attributed to the drug, but no permanent derangements have been recorded. The drug may be used safely in any stage of pregnancy though it is sometimes withheld in toxemia.

Quinacrine hydrochloride is readily absorbed from the intestine and is excreted slowly in the urine and feces. It is usually given by mouth but may also be given intravenously or preferably intramuscularly, if injection is necessary.

**Dosage.**—The following doses of quinacrine hydrochloride are administered in tablet form. Therapeutic dose in clinical malaria for adults and children over 8 years: 0.2 Gm. and 1 Gm. of sodium bicarbonate by mouth with 200 to 300 cc. of water (or an equal amount of sweetened tea or fruit juice) every 6 hours for five doses, then 0.1 Gm. three times daily for 6 days.

Children, 1 to 4 years: 0.1 Gm. three times daily for the first day, then 0.1 Gm. once daily for 6 days.

Children, 4 to 8 years: 0.2 Gm. three times daily for the first day, then 0.1 Gm. twice daily for 6 days.

Suppressive doses in malarious areas. Adults: 0.1 Gm. daily



preferably beginning 2 weeks in advance of exposure, and continuing for at least 4 weeks after last possible exposure in a malarious area.

Children: 50 mg. daily.

Suppressive doses in persons who have had attacks of vivax malaria within 6 months, and no quinacrine for 3 weeks.

Adults: 0.1 Gm. three times a day for 3 days, then 0.1 Gm. daily.

Children: 50 mg. three times a day for 3 days, then 50 mg. daily.

*Note: Each dose, therapeutic or suppressive, should be taken with a full glass of water after a meal.*

The technic of the intramuscular or intravenous administration must be studied before the method is used. Details are included in the circulars of manufacturers and in other publications.

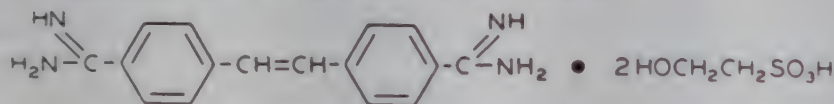
WINTHROP-STEARNs, INC.

Tablets Atabrine Hydrochloride: 50 mg. and 0.1 Gm. plain and 0.1 Gm. sugar coated.

U. S. patent 2,113,357. U. S. trademark 302,473.

## ANTIPROTOZOAN AGENTS

**STILBAMIDINE ISETHIONATE.**—4,4'-Stilbenedicarboxamide di-( $\beta$ -hydroxyethanesulfonate).—The structural formula of stilbamidine isethionate may be represented as follows:



**Physical Properties.**—Stilbamidine isethionate is a white, odorless, crystalline powder that slowly darkens on heating above 250° and melts with decomposition at 325 to 335°. It is freely soluble in water and practically insoluble in ether. The amount which dissolves in alcohol to form 100 ml. of solution is about 0.3 Gm. Stilbamidine isethionate is stable in air but is decomposed by light. The pH of a 1 per cent solution is between 5.0 and 7.0.

**Actions and Uses.**—Stilbamidine isethionate, a water-soluble salt of an aromatic diamidine base, exhibits chemotherapeutic properties useful in the treatment of certain serious protozoan and systemic fungal infections. Although stilbamidine, like certain other diamidines, also inhibits other types of micro-organisms as well as tumor cells, its use in the treatment of other infections or in neoplastic diseases has not been established. Until more conclusive evidence becomes available, use of the drug should be restricted to the treatment of systemic actinomycosis, generalized North American blastomycosis, early African trypanosomiasis (except in cases with significant spinal fluid changes) and kala-azar, especially when antimony therapy is contraindicated because of intercurrent tuberculosis. Mild leishmanial infections that are responsive to antimony therapy should not be treated with stilbamidine. It is not effective in the treatment of Torula infections.

Stilbamidine isethionate is detectable in the blood and urine in



relatively high concentrations within a few minutes after either oral administration or parenteral injection of a single maximum tolerated dose. The blood level falls rapidly within 30 minutes, despite differences in the maximum dose tolerated by various routes. A rapid fall in urinary excretion occurs after the first 2 hours. With daily administration, the amount eliminated tends to remain unchanged regardless of the dosage. Its rapid disappearance from the blood is only partially attributed to urinary excretion. The unusual adsorptive effects of the drug on proteins of the serum, plasma and other body fluids is believed to account for its rapid disappearance from the blood. Current methods for its detection are not sufficiently accurate to permit definite conclusions concerning its metabolic fate in the body. The amounts fixed in the tissue proteins or viscera have not been determined. Penetration of the meningeal barrier by the drug is poor. Intrathecal administration is not feasible because of its local irritant effect, and intramuscular injection produces local inflammation and pain at the site of administration. Concentrated solutions administered intravenously may produce thrombophlebitis.

During or immediately following intravenous injection, many or all of the following symptoms and reactions have been elicited or observed, approximately in the order of decreasing incidence: fall in blood pressure, rapid, thin pulse, facial flushing, dizziness, salivation, sweating, headache, nausea, vomiting, dyspnea, formication, syncope, lethargy, fecal and urinary incontinence and edema of the eyelids and face. These side reactions are usually transitory and disappear within 10 to 30 minutes. They are less severe with intramuscular injection and slow intravenous drip. In kala-azar, a modified Herxheimer reaction may occur within 6 hours following the first injection. The occurrence of a unique neuropathic syndrome involving progressive sensory changes in the distribution of the trigeminal nerve is a late toxic manifestation attributed to stilbamidine. Two to five months after a course of therapy, patients may gradually observe paresthesia, anesthesia, hypalgesia and numbness (usually confined to the face). Sensibility to light touch is decreased, but usually pain, temperature and pressure sense remain intact. The same findings may apply to the neck and waist. The incidence of occurrence of these late neuropathic effects is considered to be above 50 per cent. The symptoms often disappear slowly, but they may persist indefinitely. The neurotoxic effects of the drug have been sufficiently troublesome to influence physicians against using it for treatment of trypanosomiasis and leishmaniasis.

Freshly prepared solutions of the drug administered in therapeutic doses have not been associated with hepatic or renal injuries, which formerly occurred following the use of ready-made solutions exposed to ultraviolet light. However, both hepatic and renal function should be determined prior to therapy, as stilbamidine is contraindicated in hepatic or renal dysfunction. Partial deterioration of the drug is produced by the action of ultraviolet light on the unsaturated stilbene linkage. Solutions exposed to heat or light contain toxic deterioration products, but such deterioration does not occur when the drug is stored in dry form away from

heat and light. Freshly prepared solutions should be similarly protected. Following injection, patients should be warned against excessive exposure to sunlight on the premise that stilbamidine remaining in the skin may be altered and the toxic products thus formed may initiate selective nerve injury.

**Dosage.**—Stilbamidine isethionate is administered intravenously by continuous, slow drip. A freshly prepared solution of the dose to be used, dissolved in about 200 cc. of either 5 per cent dextrose in water for injection or isotonic sodium chloride solution, is infused over a period of 2 hours. Slow infusion is essential to avoid a fall in blood pressure. The solution should be protected from light by covering the container with black paper or a heavy towel.

The suggested average adult dose is 150 mg., repeated every 24 to 48 hours for a course of about 15 injections. It is advisable to initiate therapy with a 50 mg. dose, increasing this to 100 mg. for the second dose and to 150 mg. for the third dose. It is suggested that the patient be placed on a low protein, low purine-type diet, which is thought to avoid certain antidimidine effects of proteins high in arginine. The dosage and frequency of administration of the drug should be altered when necessary to meet the requirements of the individual patient. The physician should become familiar with the reactions and side effects expected from the use of stilbamidine.

THE WM. S. MERRELL COMPANY

Powder Stilbamidine Isethionate: 150 mg. ampuls.

### Antimony Compounds

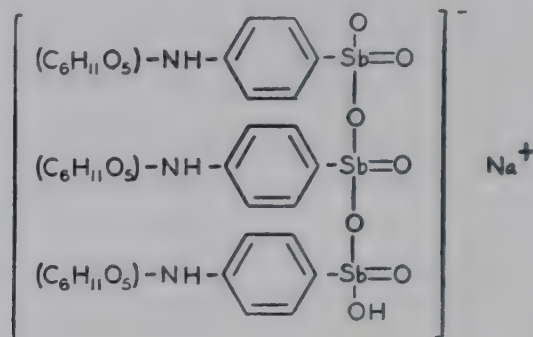
The pharmacologic effects of antimony preparations depend to some extent on the rapidity with which antimony is freed from the complex compound. All organic antimony compounds, particularly if injected rapidly into the blood stream, may produce a transient fall in systemic blood pressure, partly because output of the left ventricle is diminished and partly because the splanchnic vessels are dilated. At the same time, there is a rise in pulmonary blood pressure. Large doses depress respiration.

The mechanism by which antimony compounds cure leishmaniasis is unknown; it does not seem to be the result of a direct action on the parasites.

The pentavalent organic antimony compounds are less toxic than trivalent organic antimony compounds and may be injected intramuscularly. They are more effective in the treatment of most forms of leishmaniasis (kala-azar) but are of little value in South American leishmaniasis (muco-cutaneous) and against the helminths of schistosomiasis (bilharziasis) and filariasis. Trivalent antimony has also been preferred for the treatment of granuloma inguinale but antimony therapy in this disease has been superseded by the use of antibiotics. For the treatment of trypanosomiasis antimony compounds have been largely replaced by pentavalent organic arsenicals.



**STIBAMINE GLUCOSIDE.**—Neostam Stibamine Glucoside (BURROUGHS WELLCOME).—A nitrogen glucoside of sodium *p*-aminobenzenestibonate.—A product of incompletely defined structure prepared by the condensation of *p*-aminobenzenestibonic acid and glucose in a slightly basic solution, followed by precipitation with absolute alcohol and final drying. The rational formula provisionally assigned to stibamine glucoside is based upon the assumption of a trimer linked through the stibonic group,  $C_{36}H_{49}O_{22}N_3Sb_3Na$ . The structural formula of stibamine glucoside may be represented as follows:



**Physical Properties.**—Stibamine glucoside is an odorless, pale cream to light buff, amorphous powder. It is soluble in water. The pH of a 6 per cent solution is between 8.5 and 9.0.

**Actions and Uses.**—Stibamine glucoside shares the antiprotozoan action of other pentavalent organic antimony compounds.

Stibamine glucoside, in common with other pentavalent organic antimony compounds, produces fewer side reactions than trivalent organic antimony and may be injected intramuscularly. Reactions include vomiting (about 20 minutes after injection) and, occasionally, diarrhea. Anaphylactoid reaction, characterized by an urticarial eruption, husky voice and, in severe cases, collapse may be encountered after the sixth or seventh injection. Hepatitis is a rare but serious reaction that calls for immediate cessation of medication.

Stibamine glucoside is contraindicated in the presence of pneumonia, nephritis, jaundice or ascites.

**Dosage.**—Stibamine glucoside is administered intravenously, but may be given intramuscularly when superficial veins are not accessible. The average dose is calculated on the basis of 0.1 Gm. per 100 lb. (45.4 Kg.) of body weight, administered as a freshly prepared 4 per cent solution (0.1 Gm. in 2.5 cc. of sterile distilled water). It is rarely necessary to exceed a maximum single dose of 0.2 Gm. Injections are usually given on alternate days for a course of treatment not exceeding a total dosage of 3 Gm. per 100 lb. of body weight. This is usually sufficient to eradicate infection. A more rapidly effective method of treatment, consisting in daily injections, commences with an initial dose of 0.05 Gm. per 100 lb. of body weight. The dose is increased daily by 0.05 to 0.3 Gm. per 100 lb. body weight and then held at that amount daily until the



total dosage, not to exceed 2.55 Gm. per 100 lb. body weight, has been given. This more intensive course requires strict observation for the appearance of toxic symptoms. In treating antimony-susceptible individuals or those in whom an anaphylactoid reaction is considered likely because they have had previous treatment, it is advisable to employ an initial dose of 0.05 Gm. per 100 lb. of body weight, and to increase subsequent doses gradually as tolerance is established.

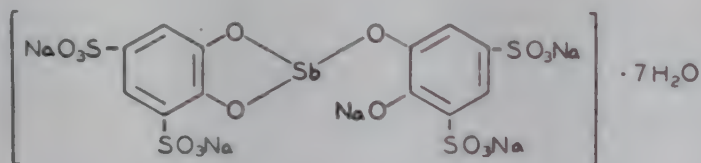
Solutions must be prepared from freshly opened containers. The solution should not be warmed for injection, nor used more than one hour after its preparation.

BURROUGHS WELLCOME & COMPANY, INC.

**Neostam Stibamine Glucoside:** 0.1 Gm. vials. Each vial contains the stated quantity of stibamine glucoside hermetically sealed under nitrogen to preserve stability.

U. S. trademark 503,747.

**STIBOPHEN-U.S.P.—Fuadin (WINTHIROP-STEARNs).**—Sodium antimony III bis-catechol-2,4-disulfonate heptahydrate.—“Stibophen contains an amount of Sb corresponding to not less than 98.5 per cent and not more than 102 per cent of  $C_{12}H_4Na_5O_{16}S_4Sb$  calculated on the anhydrous basis.” *U.S.P.* The structural formula of stibophen may be represented as follows:



**Physical Properties.**—Stibophen occurs as a white, crystalline, odorless powder. It is affected by light. It is freely soluble in water, nearly insoluble in alcohol, ether and chloroform.

**Actions and Uses.**—Stibophen is proposed for use in the treatment of granuloma inguinale and schistosomiasis (bilharziasis). Its action is reported to be more rapid and efficient in early granuloma inguinale than in the later stages when there is scar formation. It is necessary to continue the treatment for some time after all traces of the disease have disappeared. In schistosomiasis it is indicated together with iron as the treatment of choice in the intestinal stage of the disease. The iron salts should be given after the completion of the treatment and not concurrently. The anemia which is sometimes present is apparently due to a prolonged iron deficiency.

**Dosage.**—Intramuscularly (rarely intravenously), first day 1.5 cc., second day 3.5 cc., and on the third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth days 5 cc., a total of 40 cc. of 6.3 per cent solution. In a week or two following healing, the course may be repeated and thereafter the drug is given once a week and then every 14 days for several weeks to prevent relapse.

**WINTHROP-STEARNs, INC.**

**Solution Fuadin:** 5 cc. ampuls. A solution containing 63 mg. of stibophen and not more than 0.12 per cent of sodium bisulfite in each cubic centimeter.

U. S. trademark 304,950.

## Arsenic Compounds

Some of the compounds listed in this chapter contain pentavalent arsenic; in others, the arsenic is trivalent. A typical arsenic reaction is produced only by trivalent arsenic. Compounds containing pentavalent arsenic cause this reaction after they have been reduced to trivalent arsenic by the body. The rate at which this reduction occurs varies greatly with different compounds. The desirable as well as the undesirable effects produced by some of these compounds are due to the arsenic which is slowly rendered active; in others the therapeutic effects are due, at least in part, to the unaltered molecules. Arsenic therapy has proved particularly useful in diseases caused by protozoa. Inorganic arsenic kills protozoa, but the doses required are too large to be administered safely. The organic compounds are less toxic to mammals and more toxic to protozoan parasites than the inorganic preparations.

Organic arsenic compounds possess certain advantages over inorganic ones: Compounds which are effective by the liberation of arsenic free it slowly. Some organic compounds have prolonged contact with the foreign parasites because they remain in the circulating blood longer than do inorganic compounds. Other compounds of this group are specifically etiotropic; that is, they have a much greater affinity for the parasites causing the disease than they have for the tissues of the host.

Arsenic preparations used intravenously are subject to the federal law covering serums, viruses, toxins and analogous products.

### *Compounds Containing Pentavalent Arsenic*

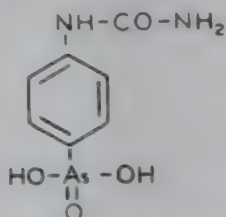
The pentavalent arsenic compounds have been used as amebicides and, more rarely, for the treatment of syphilis of the central nervous system. In the treatment of trichomonas vaginitis, the arsenicals are seldom used because there is a high risk of toxic effects without compensatory therapeutic effect. The compounds containing pentavalent arsenic are comparatively nontoxic when introduced into the animal system until changes liberate the arsenic. When they are decomposed slowly, they produce favorable effects. If the reduction takes place with greater rapidity, they may produce ordinary arsenic poisoning.

Common side reactions to the pentavalent arsenicals are gastrointestinal symptoms, hepatitis and such cutaneous disturbances as are caused by the arsphenamines, for example, urticaria, various erythemas and hemorrhagic eruptions. Intravenous administration of pentavalent arsenicals may precipitate a nitritoid reaction. Con-

traction of the visual field and blurring may occur, so that visual and color field examinations should be made prior to and during treatment so that such changes may be observed.

Arsenicals should not ordinarily be employed in the presence of hepatitis or kidney damage. Excretion of the administered arsenic is slow, and suitable rest periods must therefore be interposed in the treatment to prevent cumulative effects.

**CARBARSONE-U.S.P.**—4-Ureidobenzenearsonic acid.—“Carbar-  
sone, dried at 80° for 6 hours, contains an amount of As equivalent  
to not less than 97.5 per cent and not more than 101 per cent of  
 $C_7H_9AsN_2O_4$ .” U.S.P. The structural formula of carbar-  
sone may be represented as follows:



**Physical Properties.**—Carbar-  
sone occurs as a white, almost odor-  
less powder, having a slightly acid taste. Its saturated solution is  
acid to litmus. It is slightly soluble in water and in alcohol and  
is nearly insoluble in chloroform and in ether. It is soluble in  
solutions of alkali hydroxides and carbonates.

**Actions and Uses.**—Carbar-  
sone is used for the treatment of in-  
testinal amebiasis. It is usually administered by mouth but, in  
acute amebic dysentery or in resistant cases where motile amebas  
appear in the stools, retention enemas may be employed. Carbar-  
sone has occasionally been used in the treatment of pemphigus and  
for the local treatment of *Trichomonas vaginalis*.

**Dosage.**—Oral dosage for adults is 0.25 Gm. twice a day for 10  
days. If necessary this may be repeated following a 10-day rest  
period. For children, the dosage may be reduced according to  
weight. As a retention enema for adults, 2 Gm. of the drug dis-  
solved in 200 cc. of warm 2 per cent sodium bicarbonate solution  
may be administered following a cleansing alkaline enema every  
other night for a maximum of five doses. Because of the large  
dosage employed (a total of 10 Gm. over a period of 9 days)  
oral administration should be interrupted for this interval.

ELI LILLY & COMPANY

Powder Carbar-  
sone: 2 Gm. vials.

Pulvules Carbar-  
sone: 0.25 Gm.

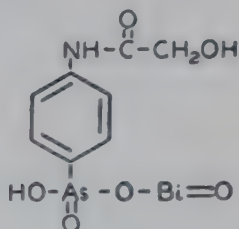
Suppositories Carbar-  
sone: 0.13 Gm.

Tablets Carbar-  
sone: 50 mg. and 0.25 Gm.

**GLYCOBIARSOL.**—Milibis (WINTHROP-STEARNs).—Bismuth Gly-



colylarsanilate.—Glycobiarsol is the product of the reaction between sodium *p*-N-glycolylarsanilate and bismuth nitrate. The structural formula of glycobiarsol may be represented as follows:



**Physical Properties.**—Glycobiarsol is an odorless, yellowish white to flesh-colored, amorphous powder which decomposes when heated. It is very slightly soluble in alcohol and water and insoluble in benzene, chloroform and ether. The pH of a saturated solution is between 2.8 and 3.5.

**Actions and Uses.**—Glycobiarsol is an amebicide recommended only for the treatment of intestinal amebiasis. Low solubility and poor absorption are responsible for its low toxicity. These properties limit its usefulness to the prevalent intestinal form of the disease. It should therefore be supplemented by other therapy in the presence of amebic hepatitis and/or deep-seated, cicatrized ulceration of the intestine.

The compound produces a characteristic bismuth effect manifested by reduced peristalsis, but in the presence of acute dysentery it must be administered in larger amounts to offset rapid elimination from the intestine. The presence of arsenic in the compound necessitates caution in its use in patients hypersensitive to arsenicals.

**Dosage.**—The average adult oral dosage recommended is 0.5 Gm three times daily; this dosage administered for a period of 7 days constitutes a single course of treatment. Further courses of treatment or change in therapy may be indicated when positive stool findings persist. Larger doses may be employed during frank diarrhea to obviate rapid elimination of the drug.

CHEMO PURO MANUFACTURING CORPORATION

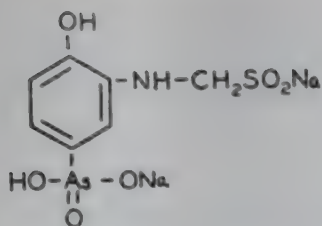
Powder Glycobiarsol: Bulk; for manufacturing use.

WINTHROP-STEARNs, INC.

Tablets Milibis: 0.5 Gm.

U. S. patent 1,934,017.

**PHENARSONE SULFOXYLATE.**—Aldarsone (ABBOTT).—Sodium 3-amino-4-hydroxyphenylarsonate-N-methanal sulfoxylate.—Phenarsone sulfoxylate consists chiefly of sodium 3-amino-4-hydroxyphenylarsonate-N-methanal sulfoxylate, admixed with sodium formaldehyde sulfoxylate, sodium chloride and sodium bicarbonate incidental to its manufacture. It contains 17.0 to 18.5 per cent of arsenic. The structural formula of phenarsone sulfoxylate may be represented as follows:



**Physical Properties.**—Phenarsone sulfoxylate is a white, odorless, amorphous powder. It is soluble in water, dilute acids, alkalis and alkali carbonates, slightly soluble in methanol and insoluble in alcohol and ether. The pH of a 5 per cent solution is between 7.0 and 7.4.

**Actions and Uses.**—Phenarsone sulfoxylate, a pentavalent arsenical, may be used in the treatment of *Trichomonas vaginalis* vaginitis and syphilis of the central nervous system.

Phenarsone sulfoxylate has comparatively low toxicity. However, because it is an arsenical, the physician should be on guard against untoward effects, particularly the serious nitritoid reactions.

**Dosage.**—For the treatment of syphilis of the central nervous system, 1 Gm. of phenarsone sulfoxylate dissolved in 10 cc. of sterile distilled water is administered intravenously once a week. The injections may be given continuously for periods of 40 to 50 weeks. Concurrent bismuth therapy may be employed during part of the phenarsone sulfoxylate treatment.

For the treatment of trichomonas vaginitis, phenarsone sulfoxylate may be administered by insufflation of the powder (with kaolin) and in the form of suppositories.

#### ABBOTT LABORATORIES

**Aldarsone with Kaolin:** 0.5 Gm. phenarsone sulfoxylate and 2.5 Gm. kaolin packaged in glass tubes suitable for use with insufflator.

**Powder Aldarsone:** 1 Gm. ampuls.

U. S. patent 2,074,757. U. S. trademark 338,986.

### Compounds Containing Trivalent Arsenic

According to Ehrlich's view, only trivalent arsenic is significantly toxic to spirochetes, trypanosomes, etc. Of compounds containing trivalent arsenic, only those are listed whose toxicity is reduced by their introduction into certain molecules. These compounds have a special affinity for certain lower organisms, while their toxicity in higher animals is comparatively low.

Administration of the drug when the patient has a full stomach or has not been prepared by catharsis may result in untoward response. Because idiosyncrasies of patients also cause reactions, it is well to start the use of arsenicals with small doses. Improper preparation or administration of the drug may add to the toxicity. If the manufacturer's directions are followed and reactions continue to occur, the cause should be sought elsewhere.

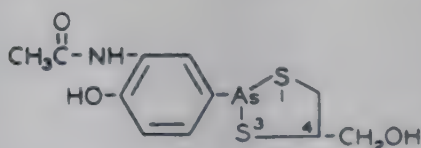
Occurrence of the Herxheimer reaction after the first injection

of the arsphenamines in active cases of syphilis is not a contraindication. This phenomenon comprises rise in temperature, headache, possible nausea, malaise and accentuation of the cutaneous and mucous membrane symptoms. Contraindications to further use are itching of the skin, urticaria, conjunctivitis, jaundice, fixed areas of dermatitis that flare up with each injection, generalized exfoliative dermatitis, purpura hemorrhagica, aplastic anemias, acute yellow atrophy and encephalitis.

The patients should be questioned prior to each administration concerning the appearance of pruritis or cutaneous eruptions following the previous injection. Urine examination should always precede readministration. Dimercaprol (BAL) has been used in the treatment of hemorrhagic encephalitis and dermatitis due to arsenotherapy. Further discussion of this technic may be found in the chapter on unclassified therapeutic agents.

Arsphenamines are contraindicated or should be used with special caution in nonsyphilitic diseases of the eye, in severe affections of the heart and blood vessels, the lungs and the kidneys and in advanced degenerative processes in the nervous system. They should also be used with caution in infants. Arsphenamine should not be used in acute luetic optic neuritis or interstitial keratitis until after preliminary antiluetic therapy with either penicillin or bismuth.

**ARSTHINOL.** — **Balarsen (ENDO).** — Cyclic 3-hydroxypropylene ester of 3-acetamido-4-hydroxydithiobenzenearsonous acid.—2-(3'-Acetamido-4'-hydroxyphenyl)-1,3-dithia-2-arsacyclopentane-4-methanol.—The structural formula of arsthinol may be represented as follows:



**Physical Properties.**—Arsthinol is a white, odorless, microcrystalline powder, with a melting point between 164 and 166°. It is very slightly soluble in ether and water. The amount which dissolves in alcohol to form 100 ml. of solution is 2.7 Gm.

**Actions and Uses.**—Arsthinol is a trivalent arsenical with indications somewhat similar to the pentavalent arsenicals which were previously available for oral use. Pentavalent arsenicals presumably are reduced to trivalent compounds in the body and act in the latter form.

Arsthinol, when administered by the oral route, has been demonstrated to be effective against intestinal amebiasis and yaws. There is no adequate evidence to indicate that the substance is effective against nonintestinal amebiasis, but it may be of value against other intestinal protozoa. However, the latter claims require further substantiation.

**Dosage.**—Arsthinol should be given in courses lasting 5 days.



The daily oral dose is 10 mg. per kilogram of body weight, with a maximum of 500 mg. in 24 hours. Ordinarily the entire daily dose is taken following breakfast.

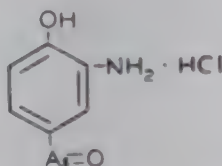
ENDO PRODUCTS, INC.

Tablets Balarsen: 100 mg.

**OXOPHENARSINE HYDROCHLORIDE-U.S.P.** — *Mapharsen* (PARKE, DAVIS). — 3-Amino-4-hydroxyphenylarsineoxide hydrochloride.—“Oxophenarsine Hydrochloride, dried in a vacuum desiccator over phosphorus pentoxide for 24 hours, contains not less than 30 per cent and not more than 32 per cent of total arsenic (As).

“Oxophenarsine Hydrochloride is usually distributed as a mixture with buffering agents and suitable substances to render its solution physiologically compatible with human blood. The label must indicate the names of the admixed substances, and the composition of the mixtures (containing Oxophenarsine Hydrochloride as the only active therapeutic agent) shall be approved by the National Institutes of Health. Mixtures contain total arsenic equivalent to not less than 92.5 per cent and not more than 107.5 per cent of the labeled amount of Oxophenarsine Hydrochloride. The mixtures also meet the requirements for *Identification*, *Completeness of solubility*, and *Packaging and storage*.

“Oxophenarsine Hydrochloride and its mixtures must be prepared in an establishment licensed for the purpose by the United States Government upon the recommendation of the Surgeon General of the United States Public Health Service. Each lot of the product before being offered for sale must comply with the toxicity, labeling, and other requirements of the National Institutes of Health, and be released by the Institutes.” *U.S.P.* The structural formula of oxophenarsine hydrochloride may be represented as follows:



**Physical Properties.**—Oxophenarsine hydrochloride is a white, odorless powder, soluble in water and in dilute alkalis and in dilute mineral acids.

**Actions and Uses.**—Oxophenarsine hydrochloride is proposed for the treatment of syphilis. It exhibits a relatively constant parasitocidal value. It is rapidly effective, particularly in early syphilis, causing the disappearance of spirochetes, healing of lesions and reversal of positive Wassermann reactions in a large percentage of cases. It is believed that an oxophenarsine compound is the immediate spirocheticidal agent formed from the arsphenamines in the host organism after injection. It thus becomes understandable that the therapeutic action of oxophenarsine hydrochloride

is about ten times greater than that of the arsphenamines. For this reason, the dosage of oxophenarsine hydrochloride, and therefore its toxic effects, are considerably less than those of the arsphenamines.

**Dosage.**—The initial intravenous dose is 0.03 Gm. for women and 0.04 Gm. for men. The dose may be increased at the second injection to 0.04 Gm. for women and 0.06 Gm. for men. The maximum dose, which should not be given any patient at the first injection, is 0.06 Gm. Injections may be given every 4 or 5 days, since the drug is excreted very rapidly from the kidneys. For children, the initial dose should not exceed 0.5 mg. per kilogram of body weight; the total dose should average between 0.5 and 1 mg. per kilogram of body weight.

#### PARKE, DAVIS & COMPANY

**Mapharsen:** 40 and 60 mg. ampuls and 0.6 Gm. multiple dose ampuls. *Caution:* These ampuls are hospital packages and represent either 10 doses at 60 mg. or 15 doses at 40 mg. Each of the ampuls of mapharsen contains the stated amount of the arsenical, oxophenarsine hydrochloride admixed with anhydrous sodium carbonate, anhydrous sucrose and ascorbic acid.

U. S. patents 2,092,028, 2,092,036, 2,221,817 and 2,280,132. U. S. trademark 299,173.

### Bismuth Compounds

Until 1921 bismuth was used mainly in the treatment of intestinal infections, in radiology and as a paste for tuberculous fistulas. Sauton and Robert in 1916 showed the value of sodium potassium bismuth tartrate in trypanosomiasis and spirillosis of fowl, and in 1921 Sazerac and Levaditi began to treat syphilis with the same drug. Bismuth seemed to have both spirocheticidal and spirochetostatic effect, and came to be used throughout the world in the treatment of syphilis. Its efficacy is between that of mercury and that of arsphenamine. Since the advent of more effective remedies, such as penicillin, bismuth is seldom employed in the treatment of syphilis; its use may be indicated in patients who are sensitive to other forms of treatment.

The best results with bismuth therapy of syphilis have been achieved with intramuscular injection. Intravenous injections are contraindicated because the therapeutic dose approaches too closely to the toxic dose. The compounds of bismuth which have the best spirocheticidal value are those that keep the level of bismuth in the blood stream continuously at the high level indicated by 0.002 Gm. or more of metallic bismuth excreted in the urine each day. The compounds injected are water-soluble salts dissolved in aqueous solution or other suitable solvents, or suspended; insoluble bismuth salts suspended in water or oils; so-called oil-soluble preparations; water-soluble and oil-suspended combinations and bismuth and arsenic compounds.

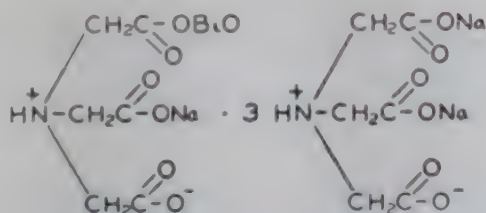
Excretion studies of various bismuth compounds used in the treatment of syphilis indicate which bismuth salts are most valuable. Utility depends on the height, course and duration of the concen-



tration of active bismuth in the tissues, especially the blood. The oil-soluble preparations have more exact dosage and more rapid absorption than insoluble suspensions of bismuth salts, but they are not absorbed and excreted as rapidly as the soluble preparations. Thus they combine some of the advantages of both the soluble and insoluble preparations. If water solutions are injected two or three times a week, the bismuth is absorbed rapidly and high concentration maintained in the blood stream. Oil suspensions effect slower but more prolonged concentration in the blood, thus requiring injections only once a week. Some oil solutions, although similar, are more rapidly absorbed. Bismuth salicylate is slowly absorbed and its bismuth effect is thereby delayed. Small amounts continue to be excreted for months after injections are stopped. It is doubtful, however, that this long excretion indicates a therapeutic level of the drug in the body.

In intramuscular injections of the bismuth salts the needle should be inserted in the upper and outer quadrant near the inner angle of the gluteal region. Having the syringe tip firmly inserted into the butt of the needle, the physician should hold the syringe loosely between the thumb and first finger, much like holding a pencil. The skin of the buttock is drawn down a little with the left hand and then with a free back and then forward motion of the right hand the needle (pointed upward and slightly toward the median plane at an angle of about  $70^\circ$  with the skin) is boldly plunged, not pushed, deep into the muscular tissue. With the needle still in place the physician should then aspirate back with the plunger of the syringe several times in order to be sure that the needle is not in a vein or in an artery. This having been ascertained, the needle butt is held firmly in place with the thumb and first finger of the left hand while the injection is made with the right hand. This will go far toward obviating many of the distressing venous emboli and arterial emboli have been reported.

**BISMUTH SODIUM TRIGLYCOLLAMATE.**—*Bistrimate* (CARROLL DUNHAM SMITH).—Sodium bismuth complex of nitrilotriacetic acid.—A double salt of sodium bismuthyl triglycollamate and disodium triglycollamate containing approximately 18.3 per cent of bismuth. The structural formula of bismuth sodium triglycollamate may be represented as follows:



**Physical Properties.**—Bismuth sodium triglycollamate is a white, odorless, crystalline powder with a somewhat salty taste. It is stable on exposure to air and light. It is very soluble in water but



insoluble in organic solvents such as acetone, benzene and ether. The pH of a 2 per cent solution is between 7.0 and 8.0.

**Actions and Uses.**—Bismuth sodium triglycollamate is effective for oral administration in the treatment of syphilis and certain diseases of the skin. It may be used alone in the management of certain forms of syphilis, but not for curative therapy of early or active syphilitic infection. It is indicated primarily when there is intolerance to other drugs or other forms of bismuth ordinarily employed for the same purpose. Bismuth sodium triglycollamate has also proved useful in some cases of lupus erythematosus, lichen planus and scleroderma. The urine should be examined frequently during the use of this drug.

Bismuth sodium triglycollamate is subject to the contraindications of bismuth preparations in general and should be discontinued in the presence of nephritis upon the appearance of albuminuria or gastro-intestinal upset.

**Dosage.**—Bismuth sodium triglycollamate is administered orally in tablet form, usually prescribed in single doses of 0.41 Gm. (75 mg. of bismuth) two or three times daily after meals to provide a total daily dosage of 0.82 Gm. (150 mg. of bismuth) to 1.23 Gm. (225 mg. of bismuth). The higher total daily dosage is desirable to maintain a satisfactory bismuth excretion level, but this may be temporarily reduced to the lower figure to overcome gastro-intestinal disturbances that are occasionally encountered.

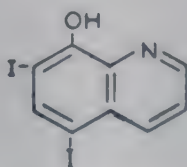
CARROLL DUNHAM SMITH PHARMACAL COMPANY

**Tablets Bistriate:** 0.41 Gm. Each tablet contains the equivalent of 75 mg. of bismuth.

U. S. patent 2,348,984.

## Iodine Compounds

**DIIDOXYHYDROXYQUINOLINE-U.S.P.** — Diodoquin (SEARLE). — Yodoxin (LEMKE). — 5,7-Diiodo-8-quinolinol. — "Diiodohydroxyquinoline, dried over sulfuric acid for 4 hours, contains not less than 60.5 per cent and not more than 64 per cent of iodine corresponding to not less than 94.5 per cent of  $C_9H_5I_2NO$ ." *U.S.P.* The structural formula of diiodohydroxyquinoline may be represented as follows:



**Physical Properties.**—Diiodohydroxyquinoline is a colorless or light yellowish to tan, micro-crystalline powder. It is odorless or has a faint odor and is stable in air. It melts with decomposition. It is almost insoluble in water and is sparingly soluble in alcohol and ether.

**Actions and Uses.**—Diiodohydroxyquinoline is used as an anti-

protozoan agent in intestinal amebiasis and in the treatment of *Trichomonas hominis* (*intestinalis*) infections.

**Dosage.**—Adults: For amebiasis, 2 Gm. daily in divided doses for a period of 20 days usually is recommended; 0.4 to 0.6 Gm. daily may be adequate in asymptomatic carriers.

B. L. LEMKE & COMPANY, INC.

Powder Yodoxin: 25 Gm., 100 Gm. and 454 Gm. bottles for compounding use; and in bulk.

Tablets Yodoxin: 0.21 Gm.

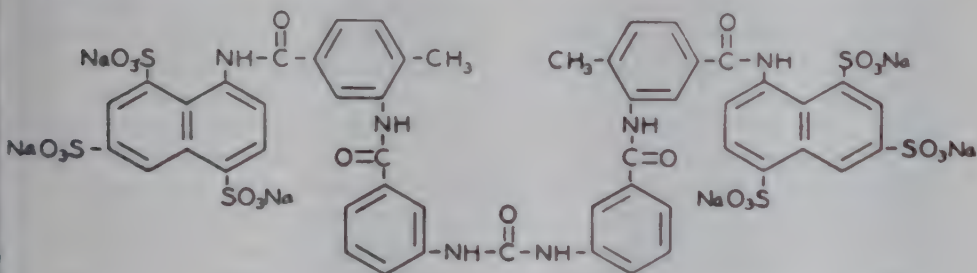
G. D. SEARLE & CO.

Tablets Diodoquin: 0.65 Gm.

U. S. trademark 336,484.

## Urea Derivatives

**SURAMIN SODIUM-U.S.P.**—Naphuride Sodium (WINTHROP-STEARNs).—Bayer 205.—Hexa-sodium bis-(*m*-aminobenzoyl-*m*-amino-*p*-methylbenzoyl-1-naphthylamino-4,6,8-trisulfonate) carbamide.—“Suramin Sodium contains not less than 97.5 per cent of  $C_{51}H_{34}N_6O_{23}S_6Na_6$ , calculated to the anhydrous basis.” *U.S.P.* The structural formula of suramin sodium may be represented as follows:



**Physical Properties.**—Suramin sodium occurs as a white or slightly pink powder. It is odorless and has a slightly bitter taste. It is very hygroscopic and is affected by light. It is soluble in water and slightly soluble in alcohol. It is insoluble in ether, in chloroform and in benzene.

**Actions and Uses.**—Suramin sodium is a trypanosomicide which dissolves readily in sterile water; the solution is neutral in reaction, odorless and almost tasteless. Only freshly made solutions should be employed. It is eliminated slowly and remains active in the body for a considerable period, offering several months' protection against reinfection with the trypanosomes of both forms (Gambian and Rhodesian) of African sleeping sickness. It is of particular value in the prophylaxis of sleeping sickness. It produces excellent results in the first stage of trypanosomiasis and a favorable influence in the second stage.

Combined treatment with suramin sodium and tryparsamide has also been recommended, since cases of invasion of the central

nervous system, which may occur early in the disease, are favorably influenced by the arsenical.

Although the drug is relatively safe when properly used, it exerts an irritant action on the kidney. Even after comparatively small doses there is frequent occurrence of albumin and sometimes hyaline and granular casts and red blood cells in the urine. However, albuminuria generally disappears spontaneously in about 6 weeks. The drug should be used with great caution in patients with renal insufficiency and albuminuria, since severe nephritis, amblyopia, amaurosis and anuria have occurred. In larger doses suramin sodium may have a hemolytic action. Occasionally, dermatitis, chill, fever, headache, nausea and pruritus may be noticed, and, more rarely, conjunctivitis, stomatitis, cutaneous hemorrhages, hemoglobinuria and agranulocytosis. Since the compound is slowly eliminated and has a cumulative action, side effects may appear after cessation of treatment. The drug should not be continued in patients who show intolerance to initial doses. During treatment the patient should be carefully checked by daily urinalyses, determination of blood pressure, frequent complete blood counts, determination of the nonprotein nitrogen content of the blood and determination of the potassium, sodium and chloride contents of the blood, so that if degeneration of the adrenal cortex occurs, it may be detected early.

**Dosage.**—Suramin sodium is usually administered intravenously in a freshly prepared 10 per cent solution. If a venipuncture is impossible, the solution may be injected intramuscularly. During the preparation of a solution, the powder is sprinkled to avoid formation of clumps on the surface of sterile distilled water. In the treatment of African sleeping sickness, the average single dose for adults is 1 Gm. weekly for a total dose of 5 to 10 Gm. Some physicians administer 1 Gm. on consecutive or on alternate days for three doses, followed by 1 Gm. weekly for two to seven additional doses, so that the total dose is again 5 to 10 Gm.

For the prophylaxis of African sleeping sickness the dose for adults is 1 Gm., for children 0.3 to 0.75 Gm. and for infants 0.15 to 0.2 Gm. The same dose is repeated in a week. At the expiration of 3 months, but not before, the prophylactic procedure may be repeated.

**WINTHROP-STEARNs, INC.**

**Naphuride Sodium: 1 Gm. ampuls.**

U. S. trademark, 398,172.



## Autonomic Drugs

The designation "autonomic drugs" is applied to drugs that either mimic or oppose the peripheral effects of nerve impulses of the autonomic (visceral efferent, vegetative, involuntary) nervous system. These drugs have been grouped into four main classes on the bases of (a) the two anatomic divisions of the autonomic system, namely, the sympathetic (thoracolumbar) and the parasympathetic (craniosacral), and (b) the two principal effects, stimulation and depression, upon the given division. Accordingly, the four classes are (1) sympathomimetic, (2) sympatholytic, (3) parasympathomimetic and (4) parasympatholytic. Since the two divisions are, on the whole, mutually antagonistic, it is seen that drugs of classes (1) and (4) have certain effects in common; thus atropine, which is parasympatholytic, and epinephrine, which is sympathomimetic, both dilate the pupil. Similarly (2) and (3) sometimes have identical effects.

The quaternary ammonium compounds produce mixed autonomic effects by partial block of nervous impulses through certain sympathetic and parasympathetic ganglia. They reduce vasospasm and arterial blood pressure but also produce loss of accommodation and decrease in gastro-intestinal motility and alter urinary bladder function.

However, the effects of these drugs vary, not only between members of different groups, but also between members of the same group. These discrepancies are partially explained by the known facts of chemical mediation of the nervous impulse. Autonomic fibers that transmit nerve impulses mediated by the epinephrine-like substance or substances called sympathin are called *adrenergic*; most postganglionic sympathetic fibers are of this type. Autonomic fibers that carry nerve impulses mediated by acetylcholine are called *cholinergic*; all postganglionic parasympathetic fibers and preganglionic fibers of both sympathetic and parasympathetic divisions are of this type. Acetylcholine has also been associated with the mediation of impulses by sympathetic nerves to sweat glands and certain vascular beds, the splanchnic fibers to the adrenal medulla, and even the cerebrospinal motor fibers to skeletal muscle.

The uncertainty that prevails regarding the exact mode and site of action of so-called autonomic drugs makes it difficult to adopt a scheme of classification that takes into account all their variable effects. One advantage in partially retaining anatomic distinctions is that they express this variation. Fibers of the sympathetic branch ramify widely through several ganglionic cells so that a diffuse discharge is possible, whereas parasympathetic fibers have terminal

ganglia near to the innervated organ so that impulses are more discrete in their effect. Furthermore, cholinesterase causes rapid destruction of acetylcholine, limiting the effect of cholinergic nerves, whereas sympathin and epinephrine disappear less rapidly and may thus be carried in the blood stream to produce the widespread effects of generalized adrenergic stimulation. It may also be significant that no gland is known to exist in the body for the elaboration of acetylcholine as the adrenal medulla does for epinephrine.

## PARASYMPATHOLYTIC AGENTS

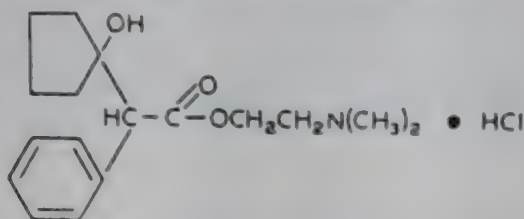
The effects of parasympatholytic (antiparasympathomimetic) agents on the body resemble the effects of cutting the parasympathetic (craniosacral) nerve supply to various parts. Drugs of the atropine-alkaloid series are classic members of this group. Familiar examples are the effects of atropine; it produces acceleration of the heart similar to that which occurs when both vagus nerves are cut, and causes dilatation of the pupil similar to that caused by cutting the oculomotor nerve. Some parasympatholytic drugs also reduce gastro-intestinal motility and secretion.

These drugs are antagonists to acetylcholine, which is liberated in ganglia and at cholinergic end organs. The enzyme cholinesterase is also found at nerve endings in the central, peripheral motor and parasympathetic nervous systems. This enzyme destroys acetylcholine and allows rapid repetitive impulse transmission by quickly hydrolyzing acetylcholine during each refractory period. Prostigmine accentuates the action of acetylcholine by inhibiting cholinesterase, and is therefore an antidote for some drugs of this series. Nicotine blocks both transmission of impulses and the action of acetylcholine. Certain newer anticholinergic drugs are curariform in nature in that toxic doses produce respiratory paralysis. Of these tetraethylammonium chloride when given intravenously or intramuscularly in moderate amounts blocks autonomic nerve transmission at the ganglia of the sympathetic and the parasympathetic alike. Moderate amounts of methantheline bromide given orally or parenterally apparently selectively block the parasympathetic transmission through ganglia; only large doses interrupt sympathetic transmission. Each of these curariform drugs is also capable of blocking the intrinsic nerve plexuses of the intestinal tract, thus producing more complete inhibition of motility and secretion than occurs with atropine.

The usefulness of atropine is diminished by the fact that it affects so many organs simultaneously; on the eye in particular, its effects continue much longer than is often desirable. Many attempts have been made to secure drugs of the atropine type with more specific actions or drugs that have a more transitory effect upon the eye. One of these drugs (homatropine) is a synthetic alkaloid analogous to atropine, the only difference being that it contains mandelic acid instead of tropic acid in combination with tropine; eucatropine is a combination of mandelic acid and a base similar to that contained in betaeucaine.



**CYCLOPENTOLATE HYDROCHLORIDE.**—Cyclogyl Hydrochloride (SCHIEFFELIN).— $\beta$ -Dimethylaminoethyl (1-hydroxycyclopentyl)-phenylacetate hydrochloride.—The structural formula of cyclopentolate hydrochloride may be represented as follows:



**Physical Properties.**—Cyclopentolate hydrochloride is a white, odorless, crystalline solid, with a melting point between 137 and 141°. It is very soluble in water, freely soluble in alcohol and practically insoluble in ether. The pH of a 1 per cent solution is 5.0 to 5.4.

**Actions and Uses.**—Cyclopentolate hydrochloride, a synthetic spasmolytic agent, produces a rapid, intense cycloplegia and mydriasis of moderate duration when instilled in the eye. Therefore, it is primarily useful for refraction studies and is effective in highly pigmented irises and for persons of all ages. The drug is also useful as a mydriatic in the management of iritis, iridocyclitis, keratitis and choroiditis. For the prevention of lenticular adhesions or in conjunction with the use of miotics, it can be employed for breaking or preventing adhesions formed during and after infections. No significant variation of intra-ocular tension has been reported from its use, but it is considered advisable to neutralize any cycloplegic in older patients in whom early, unrecognized glaucomatous changes may be present.

Cyclopentolate hydrochloride in solution does not produce any undesirable local or systemic effects following repeated instillation into the eye. It apparently is relatively nonirritating and nonsensitizing during local application. Experimental animal studies following systemic administration indicate that it has a low toxicity and exhibits about one-half the antispasmodic activity of atropine. Like other cycloplegic-mydriatic agents, caution should be observed in patients with high intra-ocular pressure.

**Dosage.**—Cyclopentolate hydrochloride is administered only in the form of ophthalmic solutions for instillation into the conjunctival sac. For refraction in Caucasians, a dose of 2 drops of a 0.5 per cent solution in each eye (each drop instilled at 5-minute intervals) for adults produces maximal cycloplegia in 30 to 60 minutes. Complete recovery occurs within 24 hours. The administration of 1 or 2 drops of 1 to 2 per cent pilocarpine nitrate reduces recovery time to 6 hours or less. In deeply pigmented eyes of dark-skinned persons, satisfactory cycloplegia may be obtained with the 0.5 per cent solution of cyclopentolate hydrochloride in about two-thirds of the cases. A 1 per cent solution of cyclopentolate hydrochloride usually produces maximal cycloplegia in Negro patients; instillation of a 2 per cent solution of pilocarpine nitrate



results in return of reading ability in 6 hours. For children, pretreatment with cyclopentolate on the day prior to examination is not usually necessary. Normally, 1 or 2 drops of a 0.5 or 1 per cent solution are instilled in each eye at the time of refraction, followed 10 minutes later by a second such application. This regime will produce satisfactory cycloplegia in all but the most refractory cases. If pretreatment in such individuals seems desirable, 1 or 2 drops of 1 per cent cyclopentolate may be instilled the evening prior to examination. Only in children with extremely dark irises has pretreatment with atropine been occasionally necessary.

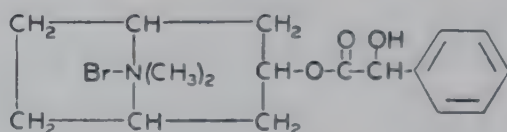
For producing paralysis of the sphincter to correct spasm caused by inflammation, 1 or 2 drops of a 0.5 per cent solution is instilled every 6 to 8 hours. For breaking or preventing lenticular adhesions secondary to infections, 1 or 2 drops of a 0.5 per cent solution is instilled, followed in 6 hours by the instillation of 2 per cent pilocarpine nitrate. Such alternate treatment should be carried out every 24 hours.

SCHIEFFELIN & COMPANY

**Ophthalmic Solution Cyclogyl Hydrochloride:** 15 cc. bottles. A solution containing either 5 or 10 mg. of cyclopentolate hydrochloride in each cubic centimeter. Preserved with 0.002 per cent benzalkonium chloride.

U. S. patent 2,554,511.

**HOMATROPINE METHYLBROMIDE-U.S.P.—Mesopin (ENDO).—Novatrin (CAMPBELL).**—The methylbromide of the alkaloid, homatropine.—The structural formula of homatropine methylbromide may be represented as follows:



**Physical Properties.**—Homatropine methylbromide occurs as an odorless, white, crystalline powder having a bitter taste. It is affected by light. It dissolves in water and in alcohol but is insoluble in ether.

**Actions and Uses.**—Homatropine methylbromide is proposed for use in the treatment of gastro-intestinal spasm and hyperchlorhydria. Animal experimentation has shown it to be less active than atropine but also less toxic.

**Dosage.**—Adults: 2.5 to 5 mg. three times daily before meals; children and infants: according to age.

CAMPBELL PHARMACEUTICAL COMPANY

**Tablets Novatrin: 2.5 mg.**

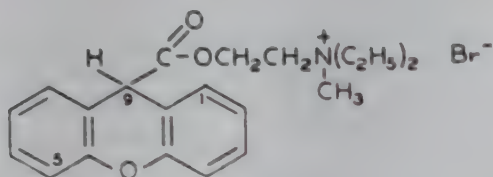
**ENDO PRODUCTS, INC.**

Elixir Mesopin: 118.3 cc., 473 cc. and 3.78 liter bottles. An elixir

containing 0.5 mg. of homatropine methylbromide in each cubic centimeter.

Tablets Mesopin: 2.5 mg.

**METHANTHELIN BROMIDE.**—**Banthine Bromide** (SEARLE).— $\beta$ -Diethylmethylaminoethyl 9-xanthenecarboxylate bromide.— $\beta$ -Diethylaminoethyl xanthene-9-carboxylate methobromide.—The structural formula of methantheline bromide may be represented as follows:



**Physical Properties.**—Methantheline bromide is a white or nearly white, odorless, microcrystalline powder with a very bitter taste. It melts between 172 and 177°. It is very soluble in water, freely soluble in alcohol and practically insoluble in ether. A 2 per cent solution has a pH between 5.0 and 5.5.

**Actions and Uses.**—Methantheline bromide, a parasympatholytic agent, produces the peripheral action of anticholinergic drugs such as atropine and the ganglionic blocking action of drugs such as tetraethylammonium chloride. Tolerated amounts of methantheline bromide exert side effects typical of atropinelike drugs, but cause less tachycardia, and also cause less postural hypotension than does tetraethylammonium chloride. Toxic doses produce a curarelike action at the somatic neuromuscular junction.

Clinical studies indicate that the drug effectively inhibits motility of the gastro-intestinal and genito-urinary tracts and, to a variable degree, diminishes the volume of perspiration and salivary, gastric, and pancreatic secretions. It also decreases mucoprotein secretion. Like atropine, it produces mydriasis and cycloplegia when applied locally to the eye or administered systemically, but until more clinical evidence becomes available, its local use for this purpose is not recommended. The value of the drug for preventing abnormal cardiac reflexes through the vagus during thoracic surgery, or as an agent for routine preoperative medication in place of atropine, requires further investigation before final conclusions can be reached.

Methantheline bromide is indicated for clinical use whenever anticholinergic spasmolytic action is desired, provided it is not contraindicated because of its atropinelike characteristics or because of a patient's intolerance to the unavoidable side effects of such therapy. It is useful as an adjunct in the management of peptic ulcer, chronic hypertrophic gastritis, certain less specific forms of gastritis, pylorospasm, hyperemesis gravidarum, biliary dyskinesia, acute and chronic pancreatitis, hypermotility of the small intestine not associated with organic change, ileostomies, spastic colon (mucous colitis, irritable bowel), diverticulitis, ureteral and urinary



bladder spasm, hyperhidrosis or control of normal sweating which aggravates certain dermatoses, and control of salivation.

Methantheline bromide produces some degree of cycloplegia and mydriasis in therapeutic doses and therefore should not be administered to patients with glaucoma. It sometimes decreases the ability to read fine print. Xerostomia (dryness of the mouth) is a common, sometimes transient, side effect. Urinary retention of varying degrees may occur in elderly male patients with prostatic hypertrophy, and some patients may have difficulty emptying the rectum. Patients with edematous duodenal ulceration may experience nausea and vomiting during initial administration of the drug. These patients should take only liquids during the institution of drug therapy. All patients should be advised of the possible occurrence of side effects. Overdosage sufficient to produce a curare-like action may be counteracted by prompt subcutaneous injection of 2 mg. of neostigmine methylsulfate.

**Dosage.**—Methantheline bromide is administered orally or parenterally by either the intramuscular or intravenous route. Parenteral administration is not advised for patients able to take the drug orally. The average initial dose for adults, oral or parenteral, is 50 mg. For patients with considerable intolerance, 25 mg. may be employed. In the management of peptic ulcer, a beginning schedule of 50 mg. three times daily before meals, and 100 to 150 mg. on retiring is suggested. However, the usual effective dose is 100 mg. four times daily, although some patients may require more or less than this amount. The dosage may be increased to tolerance, using dryness of the mouth as a guide, and adjusted to meet the individual response of patients. Maintenance dosage in peptic ulcer is usually considered to be about one-half the therapeutic level. In the management of other hypermotile or hypersecretory states, the dosage should be adjusted to the smallest amount which will relieve the symptoms. When spastic conditions are secondary to inflammatory or other organic lesions, therapy directed toward the cause should be employed whenever possible.

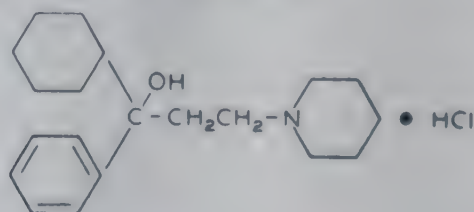
G. D. SEARLE & Co.

Powder Banthine Bromide: 2 cc. ampuls. 50 mg.

Tablets Banthine Bromide: 50 mg.

U. S. trademark 537,763.

**TRIHENYPHENIDYL HYDROCHLORIDE.**—Artane Hydrochloride (LEDERLE). — 3-(1-Piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride.—The structural formula of trihenyphenidyl hydrochloride may be represented as follows:





**Physical Properties.**—Trihexyphenidyl hydrochloride is a white, odorless solid, with a melting point between 249.0 to 249.5° (with slight decomposition). It is freely soluble in methanol and very slightly soluble in ether and in benzene. The approximate amounts which dissolve at 25° in the following solvents to form 100 ml. of solution are: 6 Gm. in alcohol, 5 Gm. in chloroform and 1 Gm. in water. The pH of a 1 per cent solution is 5.5 to 6.0.

**Actions and Uses.**—Trihexyphenidyl hydrochloride, a synthetic piperidyl compound, exhibits an atropinelike action and exerts an antispasmodic effect on smooth muscle and an inhibitory action on the parasympathetic nervous system. Thus, spasm of smooth muscle is relieved by direct action and by indirect parasympathetic release. The drug also relieves spasticity of voluntary muscle, partly because of its parasympatholytic action and partly because of action on the cerebral motor centers. Unlike atropine, the action of trihexyphenidyl is strongest in producing desirable, relaxant effects and weakest in producing undesirable side effects. Compared with atropine, trihexyphenidyl produces about one-half as intense antispasmodic action, one-third as great mydriatic action, one-eighth as much antisialogogue effect and one-tenth as much cardio-vagal inhibition.

Trihexyphenidyl hydrochloride is useful for the treatment of all forms of parkinsonism, including the postencephalitic, arteriosclerotic and idiopathic types. It reduces the muscular rigidity and relieves the depression and mental inertia characteristic of this syndrome. The drug is especially effective in reducing the rigidity produced by muscle spasm, thus increasing the ability of the patient to achieve co-ordination of muscular motions. Tremor is usually reduced, but in some patients who have been severely spastic, it may become more perceptible as spasticity is relieved. Sialorrhea is reduced but with less accompanying mouth dryness, blurred vision or mydriasis than with the use of atropine. Trihexyphenidyl is particularly useful in the treatment of arteriosclerotic parkinsonism because, unlike atropine, it usually does not tend to precipitate glaucoma.

Thus far, trihexyphenidyl hydrochloride has seldom produced severe reactions with therapeutic dosage. Some patients experience minor side effects, such as dryness of the mouth, blurring of vision, dizziness, mild nausea or nervousness. Compared with the symptoms of unrelieved parkinsonism, they are usually not troublesome and may be controlled by adjustment of dosage or time of administration. These side effects tend to decrease with continued use of the drug. The infrequent but more severe reactions of mental confusion, agitation or nausea with vomiting tend to occur in arteriosclerotic patients or in persons exhibiting other drug idiosyncrasies. Such patients must develop tolerance to the drug gradually, beginning with a smaller initial dose and increasing the dosage more slowly until an effective level is reached. If a severe reaction occurs, the drug should be discontinued for several days and then resumed at a lower dosage level. Hypertension or cardiac, liver or kidney disorders do not contraindicate use of the drug, but patients with these conditions should be carefully observed.

**Dosage.**—Trihexyphenidyl hydrochloride is administered orally. The usual initial dose is 1 mg. for the first day. If the patient is already receiving treatment with other agents, this initial dose should be substituted for a part of the current therapy. As the dosage of trihexyphenidyl is increased gradually, other medication should be decreased until the drug has replaced the former treatment or until an effective balance has been achieved. With prior therapy and in arteriosclerotic or sensitive patients, daily increments of the dose should be small until satisfactory tolerance is attained. If prior medication or unusual reactivity is not involved, the dosage is increased to 2 mg. for the second day, with subsequent increments of 2 mg. daily until a total daily amount of 6 to 10 mg. is reached. Postencephalitic patients may require as much as 12 to 15 mg. daily. At the lower level of daily dosage, the total amount can be divided into three equal parts, taken near meal times; at the higher level, a fourth dose at bedtime is required. Patients are allowed to choose whether to take the medication before or after meals. Postencephalitic patients, who have more excessive salivation, will prefer administration after meals and may require small doses of atropine sulfate as an adjuvant. Whenever the mouth becomes excessively dry, the drug can be taken before meals unless this causes nausea; if it is necessary to administer the dose after meals, dryness can be allayed by hard candy, gum or extra intake of fluid.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

**Elixir Artane Hydrochloride:** 473 cc. and 3.78 liter bottles. A flavored elixir containing 0.5 mg. of trihexyphenidyl hydrochloride in each cubic centimeter. Preserved with 0.08 per cent methylparaben and 0.02 per cent propylparaben.

**Tablets Artane Hydrochloride:** 2 and 5 mg.

U. S. trademark 500,574.

## PARASYMPATHOMIMETIC AGENTS

The effects of parasympathomimetic agents on the body resemble those seen when parasympathetic (craniosacral efferent) nerves are stimulated electrically. The effect which has been most studied is the vagal inhibition of the heart. Pilocarpine, physostigmine and acetylcholine are classed as parasympathomimetic because they slow the heart in much the same way as does the application of tetanizing current to the peripheral end of the cut vagus nerve. Di-isopropylfluorophosphate surpasses physostigmine and neostigmine in its powerful and irreversible inhibition of cholinesterase. It produces, for instance, a prolonged miosis which may prove helpful in the treatment of glaucoma.

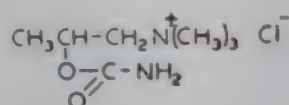
The typical parasympathetic effects, in addition to cardiac inhibition, are vasodilation in certain areas, miosis and increased gastro-intestinal motion and secretion.

It is believed that acetylcholine is the common factor in many of these processes. When injected intravenously, it has a very



powerful but transient parasympathomimetic effect; it acts so briefly because it is promptly rendered inactive by hydrolysis with cholinesterase. The electrical stimulation of parasympathetic nerves causes the appearance of acetylcholine at the neuromuscular junctions; presumably acetylcholine appears regularly during the spontaneous functioning of the postganglionic fibers of the parasympathetic nerves, and is regularly kept from accumulating by the cholinesterase. Since physostigmine acts by opposing the cholinesterase, it is a parasympathomimetic drug. In the case of pilocarpine, muscarine and some others, however, it has been necessary to suppose that they act directly on the same receptive structure as does acetylcholine. Various choline derivatives have been synthesized that are sufficiently stable in the presence of cholinesterase to produce useful parasympathetic activity. Unlike acetylcholine, some are effective when administered orally and do not share its "nicotine" action. Methacholine is perhaps the best example of this class.

**BETHANECHOL CHLORIDE.**—Urecholine Chloride (SHARP & ДОХМЕ).— $\beta$ -Methylcholine carbamate chloride.—Urethane of  $\beta$ -methylcholine chloride.—The structural formula of bethanechol chloride may be represented as follows:



**Physical Properties.**—Bethanechol chloride is a white, crystalline solid with an aminelike odor. It melts between 217 and 220° with decomposition. It is very soluble in water, freely soluble in alcohol and practically insoluble in chloroform, benzene and ether. The pH of a 0.5 per cent solution is between 5.5 and 6.3.

**Actions and Uses.**—Bethanechol chloride has pharmacologic properties similar to those of methacholine chloride but differs from acetylcholine in that it exhibits little if any ganglionic stimulating action and is not destroyed by choline esterase. It is less toxic than some other esters of choline but is also less active.

Bethanechol chloride is useful in the treatment of conditions which are relieved by stimulation of the parasympathetic nervous system. It has been used successfully in the treatment of gastric retention following vagotomy, in postoperative urinary retention and in postoperative abdominal distention.

Although the drug has been tried in a number of other conditions which sometimes respond to parasympathetic stimulation, its precise role is not fully established. It may, however, be tried in such disorders as megacolon, adynamic ileus accompanying severe trauma, acute infections, neurogenic disorders, neurogenic atony of the urinary bladder with retention and gastric atony and retention following gastric surgery.

**Dosage.**—The optimum method of administration and the dosage must be determined for the individual. Mild or moderately severe



disorders may respond to oral therapy, whereas severe maladies may require subcutaneous injection of the drug.

Oral doses of 10 to 30 mg. of bethanechol chloride three or four times daily meet most needs. The effect of the drug is sometimes apparent within 30 minutes.

The drug should never be given intravenously or intramuscularly. It may be administered *subcutaneously* to patients who do not respond to oral therapy or to those whose physical condition precludes it. The usual subcutaneous dose is 5 mg. (1 cc.), although some patients respond satisfactorily to as little as 2.5 mg. (0.5 cc.). It is suggested that the *minimum effective dose* be determined in each case by injecting 2.5 mg. initially and following this with a second, third or fourth dose of similar size at 15-minute to 30-minute intervals if neither satisfactory response nor disturbing side effects result. The optimum dose thus determined may be repeated three or four times daily, if required. Subcutaneous injection of single doses up to 10 mg. may be necessary to produce a satisfactory response, but such doses should be given only after adequate trial with doses of 2.5 to 5 mg. Unpleasant and occasionally severe side effects may occur following subcutaneous doses of 5 to 10 mg. All effects of the drug can be abolished promptly by subcutaneous or intravenous injection of 0.6 mg. atropine sulfate.

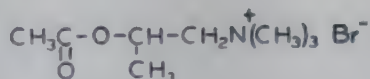
SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Solution Urecholine Chloride:** 1 cc. ampuls. A solution containing 5 mg. of bethanechol chloride in each cubic centimeter.

**Tablets Urecholine Chloride:** 5 mg.

U. S. trademark 389,037.

**METHACHOLINE BROMIDE.**—Mechoyl Bromide (SHARP & DOHME).—(2-Hydroxypropyl)trimethylammonium bromide acetate.—The structural formula of methacholine bromide may be represented as follows:



**Physical Properties.**—Methacholine bromide is a white, crystalline, very hygroscopic powder with a slight fishy odor. It melts between 146.5 and 148.5°. It is readily soluble in alcohol and water and insoluble in benzene and ether. The pH of a freshly prepared 5 per cent solution is about 4.6.

**Actions and Uses.**—The actions of methacholine bromide are the same as those of methacholine chloride, but because it is less hygroscopic than the latter salt, it is suitable for oral use in tablet form. For those skilled in the technic of ion transfer (iontophoresis), the local application of the chloride by this method is preferable in the treatment of chronic ulcers, scleroderma, Raynaud's disease and other vasospastic conditions of the extremities, except possibly the

management of vascular spasm from exposure to moderate cold.

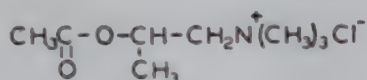
**Dosage.**—Methacholine bromide is administered in doses of 0.2 to 0.6 Gm. two or three times daily; 50 mg. to 0.1 Gm. may be sufficient to overcome vascular spasm due to moderate exposure to cold, but in chronic ulcers, scleroderma and Raynaud's disease the larger doses are required. With patients in whom a total daily dose of 2 Gm. of the drug is not effective, oral treatment should be abandoned in favor of the use of methacholine chloride by subcutaneous injection or local application by the method of ion transfer (iontophoresis).

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

Tablets Mecholyl Bromide: 0.2 Gm.

U. S. trademark 318,783.

**METHACHOLINE CHLORIDE-U.S.P.**—Mecholyl Chloride (SHARP & DOHME).—(2-Hydroxypropyl)trimethylammonium chloride acetate.—The structural formula of methacholine chloride may be represented as follows:



**Physical Properties.**—Methacholine chloride occurs as colorless or white crystals, or as a white, crystalline powder possessing a slight odor. It is very deliquescent. Its solutions are neutral to litmus paper. It is readily soluble in water and alcohol, insoluble in benzene and ether.

**Actions and Uses.**—Methacholine chloride is useful, by subcutaneous injection only, in the treatment of selected cases of paroxysmal auricular tachycardia not responding to the usual therapeutic measures. In the palliative local treatment of chronic rheumatoid (atrophic) arthritis it is used by the local method of ion transfer (iontophoresis) only. In the treatment of chronic ulcers, Raynaud's disease, scleroderma and other vasospastic conditions of the extremities it is used preferably by the local method of ion transfer (iontophoresis) but also by oral or subcutaneous administration when the electrical method cannot be employed. The drug is inferior to quinidine for the prevention of attacks of paroxysmal auricular tachycardia. It is of no apparent value in the treatment of other forms of tachycardia in auricular fibrillation although there is a possibility of inducing transitory heart block, followed by resumption of normal rhythm. The drug is not useful in the treatment of bladder dysfunction, abdominal distention, atonic constipation, pelvic inflammation, functional dysmenorrhea, atropic rhinitis, glaucoma or hypertension. (Also see the monograph on methacholine bromide.)

**Dosage.**—Considerable variation in the oral dosage requirements is expected because methacholine chloride is to some extent destroyed by the gastric juice. The therapeutically effective oral dose usually ranges from 0.2 to 0.5 Gm. two or three times a day, ad-



ministered by dissolving in a little water to which milk may be added to disguise the bitter taste. In overcoming vascular spasm due to moderate exposure to cold, oral doses of 50 mg. to 0.1 Gm. have been found effective. In Raynaud's disease, scleroderma and ulcers, the effective oral dose may be somewhat higher.

The subcutaneous dose should be limited to 10 mg. on the first injection to test the patient's tolerance. If tolerated, the dose may be cautiously increased up to 25 mg. This dose is usually adequate for injection when this method is employed in the treatment of Raynaud's disease, scleroderma, chronic ulcers and other vasospastic conditions of the extremities. In paroxysmal auricular tachycardia, 20 to 40 mg. is injected subcutaneously. If a second injection is required, it is advisable to wait about 10 to 20 minutes until the effect of the first has disappeared, and then to give the second dose only after cautious, gentle massage at the site of the first injection. Cumulative effects or effects of overdosage may be quickly abolished by an injection of 0.6 mg. of atropine sulfate.

For application of methacholine chloride by the method of ion transfer (iontophoresis) it is customary to use a 1:200 to 1:500 solution of the drug in distilled water. The solution is applied by moistening the positive electrode fabric which is placed over or near the part to be treated. The strength and duration of the galvanic current regulates the dosage and should always be applied gradually and within the amount comfortably tolerated by the patient. The patient should be instructed to report any sensation of excessive heat or burning. If this occurs, the treatment should be stopped and inspection made to determine if an electrode is improperly placed. The initial treatment should not exceed 5 to 10 ma. for 30 minutes. Subsequent treatments usually require from 25 to 30 ma. applied for 20 to 30 minutes. When several parts are involved, each treatment should be restricted to a limited area such as one hand or one joint. Three or four days is the most satisfactory interval between treatments. The number of treatments necessary to obtain results varies with the patient and with the type of lesion. In Raynaud's disease and scleroderma, ten or more treatments may be necessary to secure improvement; in chronic rheumatoid arthritis the treatments may be reduced to intervals of a week after the first four to six treatments; in varicose indolent and gangrenous ulcers, treatments may be given daily at the start to promote granulation of tissue and then reduced after the first few treatments to two or three times a week. During treatments by ion transfer (iontophoresis) the patient should be covered and protected from drafts and for about 30 minutes after each treatment should be kept quiet and warm. He may then be permitted to resume protected activity.

Idiosyncrasy to methacholine chloride may result in difficulty in breathing. In this event treatment should be stopped and the patient raised to a sitting position. If untoward symptoms do not subside, atropine sulfate should be given at once hypodermically.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

Powder Mecholyl Chloride: 1 Gm. and 10 Gm. bottles for the



preparation of solutions for oral administration and for ion transfer (iontophoresis).

**Powder Mecholyl Chloride:** 25 mg. ampul for the preparation of solutions for subcutaneous injection.

U. S. trademark 318,783.

## Cholinergic Agents

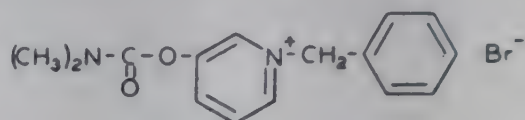
Pharmacologic experiments indicate that benzpyrinium bromide and neostigmine compounds possess some of the properties of the closely allied drug physostigmine. Their actions and uses, therefore, are similar to those of physostigmine, but the synthetic preparations are more stable. They are as active as physostigmine in stimulating intestinal peristalsis and have a similar but diminished miotic activity. There is no satisfactory evidence that the symptoms produced by toxic doses of benzpyrinium bromide or neostigmine salts are any less severe than those produced by comparable doses of physostigmine or its salts. This latter fact becomes especially important when it is considered that benzpyrinium bromide and neostigmine preparations are used by subcutaneous and intramuscular injection, since they are four to six times as toxic as physostigmine when injected subcutaneously in the rabbit. Atropine is the antidote to neostigmine.

Neostigmine preparations and benzpyrinium bromide are used for the treatment of atony of the intestinal and bladder musculature and for the symptomatic control of myasthenia gravis. Their use for the treatment of intestinal and bladder atony is based on their vagotonic activity; because of their anticurarelike action, they are applied in the symptomatic treatment of myasthenia gravis. They are also credited with mild laxative action but their use solely for that purpose is not advisable. The use of neostigmine methylsulfate has been recommended to antagonize the action of curari-form drugs.

Neostigmine methylsulfate or benzpyrinium bromide is injected for the treatment of delayed menstruation and as a test for early pregnancy upon the unestablished concept that the delay is the secondary result of diminished vascular responsiveness to acetylcholine rather than a primary endocrine disturbance. Although the drugs appear safe for this purpose and are free of abortifacient action, they are unsatisfactory as a presumptive test for pregnancy because they fail to induce bleeding not only in the presence of pregnancy but also in the presence of organic systemic disease, endocrine disorders, etc., not associated with pregnancy. However, these drugs may be useful as a screening test for pregnancy; in the event of absence of bleeding following their administration the positive diagnosis of pregnancy should not be made until the result is checked by one of the acceptable biologic tests for pregnancy. They are recommended only for the induction of bleeding in temporary functional amenorrhea.

These agents are available only in the form of their salts.

**BENZPYRINIUM BROMIDE.**—**Stigmonene Bromide** (WARNER-CHILCOTT).—1-Benzyl-3-(dimethylcarbamoyloxy) pyridinium bromide.—The structural formula for benzpyrinium bromide may be represented as follows:



**Physical Properties.**—Benzpyrinium bromide is a white to slightly yellow crystalline powder with almost no odor. It melts between 114 and 120°. It is very soluble in alcohol and water and practically insoluble in ether. A 1 per cent solution of benzpyrinium bromide has a pH between 4.5 and 5.5.

**Actions and Uses.**—Benzpyrinium bromide has the same actions and uses as neostigmine. See the general statement on cholinergic agents.

**Dosage.**—For the treatment of postoperative abdominal distention, 1 cc. of the 1:500 solution (2 mg.) is administered by intramuscular injection, followed by a small, low enema 20 to 30 minutes after the injection. Intramuscular injection is repeated every 2 to 3 hours until the desired effect is obtained.

For the treatment of postoperative urinary retention, 1 cc. of the 1:500 solution (2 mg.) is administered by intramuscular injection, and heat (hot-water bottle, electric pad) is applied to the lower abdomen. The intramuscular injection is repeated every 2 to 3 hours until satisfactory micturition occurs or catheterization becomes necessary. In the latter instance, therapy should be continued until the patient voids spontaneously.

For the treatment of simple, delayed menstruation, 1 cc. doses of the 1:500 solution (2 mg.) are given by intramuscular injection once daily for 1 to 3 successive days. In the absence of endocrine disturbance, organic pelvic lesions or systemic disorders, menstrual flow may be evoked with the first or second injection, and further therapy is discontinued. If no menstruation occurs 8 days after the third injection, pregnancy or organic disease should be considered, and appropriate diagnostic procedures should be undertaken.

As four times the volume of the 1:500 (2 mg.) solution is required when the 1:2,000 (0.5 mg.) solution is used, the former concentration has been found to be more convenient.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

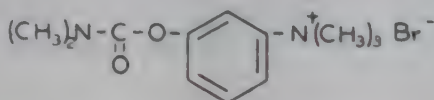
**Solution Stigmonene Bromide 1:500:** 1 cc. ampuls. A buffered, saline solution containing 2 mg. of benzpyrinium bromide in each cubic centimeter.

**Solution Stigmonene Bromide 1:2,000:** 1 cc. ampuls. A solution containing 0.5 mg. of benzpyrinium bromide in each cubic centimeter.

U. S. patent 2,489, 247. U. S. trademark 557,370.



**NEOSTIGMINE BROMIDE-U.S.P.**—Prostigmin Bromide (HOFFMANN-LAROCHE). — (*m*-Hydroxyphenyl)trimethylammonium bromide dimethylcarbamate.—“Neostigmine Bromide, dried at 105° for 3 hours, contains not less than 98 per cent of C<sub>12</sub>H<sub>19</sub>BrN<sub>2</sub>O<sub>2</sub>.” *U.S.P.* The structural formula of neostigmine bromide may be represented as follows:



**Physical Properties.**—Neostigmine bromide is a white, crystalline powder, odorless and of bitter taste. Its solutions are neutral to litmus paper. One gram of neostigmine bromide dissolves in about 1 cc. of water. It is soluble in alcohol and practically insoluble in ether.

**Actions and Uses.**—See the general statement on cholinergic agents. Neostigmine bromide is used orally for the treatment of myasthenia gravis. The bromide is used in the form of oral tablets as it is comparatively nonhygroscopic. It also is employed in an ophthalmic solution as a miotic for the management of glaucoma.

**Dosage.**—For myasthenia gravis, an initial dose of 15 mg. three times a day after meals. This may be increased to 30 mg., and the interval may be diminished to every 2 or 3 hours if necessary. Dosage should be kept at the minimum necessary to control symptoms without side effects. If more than 150 to 270 mg. per day is required, oral administration should be supplemented with neostigmine methylsulfate parenterally or with other drugs. Should unpleasant side effects occur, they often may be controlled with atropine sulfate.

A 5 per cent solution is used for ophthalmic instillation in the treatment of glaucoma, but in some cases half this strength may be adequate. Several drops are usually required as a single dose, and this should be repeated as often as necessary to maintain intra-ocular tension within normal limits.

HOFFMANN-LAROCHE, INC.

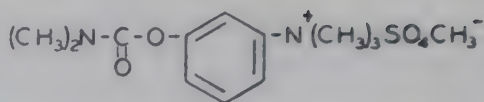
**Ophthalmic Solution Prostigmin Bromide 5%:** 7.5 cc. dropper bottles. A solution containing 50 mg. of neostigmine bromide in each cubic centimeter. Buffered with 1 per cent boric acid. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

**Tablets Prostigmin Bromide:** 0.015 Gm.

U. S. trademark 293,889 and 421,595.

**NEOSTIGMINE METHYLSULFATE-U.S.P.**—Prostigmin Methylsulfate (HOFFMANN-LAROCHE). — (*m*-Hydroxyphenyl)trimethylammonium methylsulfate dimethylcarbamate.—“Neostigmine Methylsulfate, dried at 105° for 3 hours, contains not less than 98 per cent of C<sub>13</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub>S.” *U.S.P.* The structural formula of neostigmine methylsulfate may be represented as follows:





**Physical Properties.**—Neostigmine methylsulfate is a white, crystalline powder. It is odorless and has a bitter taste. Its solutions are neutral to litmus paper. One gram is soluble in about 10 cc. of water. It is less soluble in alcohol. It melts between 142 and 145°.

**Actions and Uses.**—See the general statement on cholinergic agents.

**Dosage.**—Prevention of postoperative distention: Small doses of the 1:4,000 solution are administered subcutaneously or intramuscularly at frequent intervals. Injections are begun as soon as possible and repeated in 1 cc. doses every 4 to 6 hours until the second or third postoperative day. Treatment of postoperative distention: Usually one or two ampuls of the 1:2,000 solution, as required, are administered subcutaneously or intramuscularly. Experimental use in the treatment of myasthenia gravis: Only one ampul of the 1:2,000 solution is administered initially, the size and frequency of the subsequent doses to be indicated by the degree and duration of the response to the initial dose. The course of treatment usually consists of one to four ampuls (0.5 to 2 mg. of neostigmine methylsulfate).

For induction of bleeding in temporary functional amenorrhea, 1 mg. (1 cc. of 1:1,000 solution) is injected daily for 3 successive days. If no bleeding occurs within 72 hours after the third injection, this is considered presumptive evidence of nonfunctional amenorrhea. In this case further efforts to induce bleeding should be abandoned until all nonfunctional causes are ruled out.

To combat the effects of overdose of curariform drugs, 1 or 2 cc. of the 1:2,000 solution is used.

HOFFMANN-LA ROCHE, INC.

Solution Prostigmin Methylsulfate 1:2,000 and 1:4,000: 1 cc. ampuls.

U. S. trademark 293,889 and 421,595.

LINCOLN LABORATORIES, INC.

Solution Neostigmine Methylsulfate 1:2,000: 10 cc. vials. A buffered, isotonic solution containing 0.5 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.45 per cent phenol.

E. S. MILLER LABORATORIES, INC.

Solution Neostigmine Methylsulfate 1:1,000: 10 cc. vials. An isotonic solution containing 1 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.02 per cent propylparaben and 0.18 per cent methylparaben.

Solution Neostigmine Methylsulfate 1:2,000: 1 cc. ampuls.

THE VITARINE COMPANY, INC.

Solution Neostigmine Methylsulfate: 5 cc. vials. A solution con-

taining 1 mg. of neostigmine methylsulfate in each cubic centimeter. 1 cc. ampuls and 10 cc. vials. A solution containing 0.5 mg. of neostigmine methylsulfate in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

## SYMPATHOLYTIC AGENTS

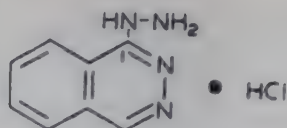
The effects of sympatholytic agents (antisympathomimetic) on the body resemble the effects of cutting the sympathetic (thoracolumbar visceral efferent) nerve supply. Such drugs are antagonists of epinephrine, and accordingly are often referred to as adrenolytic agents. They slow the heart, lower blood pressure by extensive vasodilatation and increase gastro-intestinal muscle tone. Among the drugs which block the vasoconstricting and blood pressure elevating effects of epinephrine are ergotoxin, piperoxan (F 933 or benodaine) and yohimbine. Ergotamine tartrate and F 883 diethylaminomethyl-1,4-benzodioxan more potently depress or block sympathetic reflexes. Various well-known preparations of ergot also exhibit this type of action in some degree; they are described in the chapter on oxytocics. Although a sympatholytic drug by strict definition must be adrenolytic, the reverse is not necessarily true. Certain drugs may be adrenolytic only, since adrenolysis uniformly requires less potency or lower dose than that necessary for sympatholysis.

Currently, the best known of these drugs are piperoxan (2-[1-piperidylmethyl]-1,4 benzodioxan) (F 933 or benodaine); dibenzyl- $\beta$ -chloroethylamine hydrochloride (dibenamine hydrochloride); 2-benzyl-2-imidazoline hydrochloride (priscoline hydrochloride) and 2-[N-p'-tolyl-N-(m'-hydroxyphenyl) aminomethyl] imidazoline (regitine).

Clinical reports suggest that intravenously administered 2-(1-piperidylmethyl)-1,4-benzodioxan (benodaine) reduces the blood pressure of patients having hypertension caused by circulating adrenalin from pheochromocytoma. Small intravenous, intramuscular or oral doses of 2-[N-p'-tolyl-N-(m'-hydroxyphenyl) aminoethyl] imidazoline (regitine) evidently similarly reduce blood pressure and aid diagnosis of pheochromocytoma. Dibenzyl- $\beta$ -chloroethylamine (dibenamine) administered intravenously blocks and reverses the pressor action of epinephrine and interrupts vasomotor reflexes for periods as long as 24 hours. 2-Benzyl-2-imidazoline hydrochloride (priscoline hydrochloride) and 2-[N-p'-tolyl-N-(m'-hydroxyphenyl) aminoethyl] imidazoline (regitine) are effectively administered orally in patients with certain circulatory disorders of the extremities, an action described as sympatholytic. These and similar drugs are receiving extensive clinical trial and are gradually coming into general use.

**HYDRALAZINE HYDROCHLORIDE.**—Apresoline Hydrochloride (CIBA).—1-Hydrazinophthalazine hydrochloride.—The structural formula of hydralazine hydrochloride may be represented as follows:





**Physical Properties.**—Hydralazine hydrochloride is a white, odorless, crystalline powder, with a melting point between 270 and 280° (with decomposition). It is very slightly soluble in ether. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 0.2 Gm. in alcohol and 4.4 Gm. in water. The pH of a 2 per cent solution is 3.5 to 4.5.

**Actions and Uses.**—Hydralazine hydrochloride, a derivative of phthalazine, is an antipressor drug which exerts chiefly a central action on the midbrain. It possesses a moderate degree of adrenergic (adrenolytic and sympatholytic) blocking action against the pressor effects of epinephrine and levarterenol. The drug increases blood flow through the kidney, diminishes cerebral vascular tone and reduces both diastolic and systolic blood pressure. Hydralazine may inhibit the pressor actions of angiotonin (hypertensin), serotonin, pherentasin and possibly other endogenous factors considered important in causing hypertension. It also inhibits the hormonal-cerebral vasopressor substance which may participate in varying degrees in more than one form of hypertensive disease and which is not affected by more potent adrenergic blocking agents. The capacity to inhibit a pressor substance of cerebral origin may explain the drug's effectiveness in neurogenic hypertension not benefited by extensive lumbodorsal sympathectomy.

Hydralazine helps control essential and early malignant hypertension. Its efficacy is often greater in acute, more severe, non-terminal phases of these disorders. In advanced pathologic changes of the kidney (chronic renal hypertension or chronic glomerulonephritis), the effectiveness of the drug is diminished considerably. Although kidney function improves in some patients, evidence is lacking to indicate that the drug effects any anatomic alteration in patients with severe and progressive cardiovascular disease. More experience is necessary to determine whether the capacity of hydralazine to lower elevated pressure in early, severe hypertension will delay development of vascular damage. Worthwhile results may be expected in the toxemias of pregnancy. Preliminary studies indicate some beneficial effects in acute glomerulonephritis. Thus, hydralazine is a useful adjunct in the control of diverse forms of hypertension, with due consideration to the environmental, dietary and psychic factors involved.

Although true tolerance to the drug has not been demonstrated, blood pressure may rise occasionally during treatment. When this occurs, it may be advisable to discontinue therapy for a week, then resume it, prescribing small doses as for initial treatment.

Because the toxicity of hydralazine is low, serious untoward effects are seldom encountered. Studies on experimental animals have not revealed evidence of chronic toxic effects on the tissues. Clinically, postural hypotension and circulatory collapse may pre-



cede a fall in blood pressure, but severe reactions of this kind are relatively rare. The secondary effects of a reduction in blood pressure per se may cause tachycardia, headache, dizziness, faintness, palpitation, angina, numbness and tingling of extremities, malaise, depression, disorientation and anxiety. In addition to these side effects, the drug also may produce nausea, vomiting and mild periorbital, ankle, genital or other localized edema. Giant urticaria, relieved when the drug is withdrawn, also has been reported. In most patients, side effects usually disappear after the first 2 weeks of medication but may persist with continued therapy or reappear upon increase of the dosage.

*The physician must be thoroughly familiar with the characteristics of hydralazine before prescribing or administering the drug. Only with such understanding can the maximal benefit, consistent with minimal untoward effects, be fully realized. Use of the drug in conjunction with other potent hypotensive drugs should not be attempted until there is further evidence by which to weigh the possible usefulness of combined therapy against its potential dangers.*

Caution is advised in the prolonged administration of large doses as they have been reported to produce, in some patients, an apparently toxic response resembling either early rheumatoid arthritis or, what is regarded as a more severe phase of the same syndrome, acute systemic lupus erythematosus. The milder rheumatic phase usually disappears when the drug is withdrawn or the dosage reduced. The severe erythematous form has been controlled with cortisone and corticotropin.

**Dosage.**—Hydralazine hydrochloride usually is administered orally but may be injected parenterally (intramuscularly or intravenously) when the drug cannot be given by mouth. By either route, the dosage must be individualized in accordance with the response of the patient.

In the ambulatory patient, therapy should be initiated by the oral route, and the patient carefully instructed by the physician concerning the subjective effects which are produced. Headache and/or palpitation usually are experienced within 12 to 24 hours following the initial dose. These symptoms usually disappear spontaneously, with no change in dosage, within 7 to 10 days after starting treatment.

The initial dose for moderate to severe hypertension should be 10 mg., given four times daily, after each meal and at bedtime, to make a total daily dose of 40 mg. Individual doses should be spaced equally, and the total of 40 mg. per day should be continued for the first 2 to 4 days, unless contraindicated because of severe or distressing side effects. The dose may be increased to 25 mg. four times daily for the balance of the first week. During the second week, the dose may be increased to 50 mg. four times daily (total daily dose of 200 mg.). If side effects are absent or minimal and the blood pressure can be reduced to a more desirable level, the single dose may be augmented by 10 or 25 mg. increments every 5 to 7 days. Most patients obtain maximal benefit from the schedule of 100 mg. four times daily (total daily dose of

400 mg.). However, some patients are best stabilized with as little as 100 mg. per day in divided doses; others may tolerate as much as 600 mg. per day. If tolerance develops, the drug should be withdrawn for 1 week and then resumed at the lowest effective level.

In hospitalized patients with more severe types of hypertensive disease, therapy also is initiated by the oral route at a dose of 25 mg. every 6 hours for the first 24 hours. Thereafter, individual doses are increased by 25 mg. daily until the desired effect is obtained. Intervals between individual doses should be equal and no less than 4 hours apart. The same management of side effects and tolerance for the ambulatory patient applies to the hospitalized patient.

Parenteral injection may be used to initiate therapy in hospitalized patients with severe hypertension who are unable to take the drug orally. The usual parenteral dose is 20 to 40 mg. intravenously or intramuscularly every 4 to 6 hours, depending upon the patient's response. In patients with extensive renal damage, a smaller initial dose may be indicated. The blood pressure, which should be checked frequently to detect any precipitous drop, will act as a guide to individual dosage. Pressure may begin to decline within 2 or 3 minutes after injection; the average maximal fall occurs within 10 to 80 minutes. When the measured fall is not as large as desired, subsequent individual doses may be increased gradually, provided absorption of the initial dose has not been delayed. It is usually possible to shift to oral therapy within 24 to 48 hours. In cases of pre-eclampsia or eclampsia, the blood pressure may fall dramatically to normal levels within 5 to 10 minutes after the intravenous injection of 20 to 40 mg. It is advisable to inject 20 mg. as the initial dose and to follow with another injection if further reduction of blood pressure is desired. The effect may persist 6 to 24 hours. Additional injections may be given and, as soon as feasible, the patient shifted to oral therapy with the schedule ordinarily followed for hospitalized patients. In hypertensive episodes associated with acute glomerulonephritis, intramuscular injections of 0.25 mg. per kilogram of body weight are usually effective in reducing blood pressure. Injections may be repeated as necessary every 4 to 6 hours.

#### CIBA PHARMACEUTICAL PRODUCTS, INC.

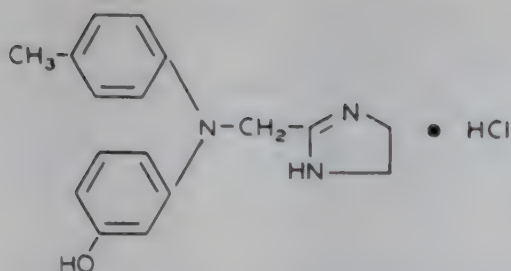
**Solution Apresoline Hydrochloride:** 1 cc. ampuls. A solution containing 20 mg. of hydralazine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Tablets Apresoline Hydrochloride:** 10, 25, 50 and 100 mg.

U. S. patent 2,484,029.

**PHENTOLAMINE HYDROCHLORIDE.** — Regitine Hydrochloride (CIBA). — 2-{[N-(*m*-Hydroxyphenyl)-*p*-toluidino]methyl}-2-imidazoline hydrochloride.—The structural formula of phentolamine hydrochloride may be represented as follows:





**Physical Properties.**—Phentolamine hydrochloride is a white or slightly off-white, odorless, bitter powder. It is very slightly soluble in chloroform and practically insoluble in acetone and ethyl acetate. The amounts that dissolve in the following solvents to form 100 ml. of solution are: 0.85 Gm. in alcohol and 2 Gm. in water. Aqueous solutions of phentolamine hydrochloride are unstable. The pH of the 1 per cent solution is 4.5 to 5.5.

**Actions and Uses.**—Phentolamine hydrochloride, a salt of phentolamine base, is suitable for oral administration and acts as a potent adrenergic blocking agent, producing adrenolytic and sympatholytic effects.

Experimentally, phentolamine blocks the peripheral effects associated with electrical stimulation of sympathetic nerves (sympatholytic action). In comparatively small amounts, it effectively reverses the hypertensive action of injected epinephrine and suppresses the pressor response to levarterenol (adrenolytic action). This antiadrenergic action constitutes the basis for the use of phentolamine salts in the diagnosis and control of hypertension caused by pheochromocytoma and in the treatment of certain vascular diseases in which blood flow to ischemic extremities can be increased by adrenergic blockade. In certain cases, the drug has been shown to be beneficial in the treatment of the sequelae of frostbite and immersion foot and has produced favorable responses in other vasospastic conditions, including Raynaud's disease and vasospasm associated with trophic ulcers of the extremities. It also has proved valuable in some patients as an antihypertensive agent, particularly in the management of hypertensive emergencies or as an adjunct in the treatment of chronic arterial hypertension.

Because of its less ready solubility and the temporary stability of aqueous solutions of phentolamine salts, phentolamine hydrochloride (in contrast to phentolamine methanesulfonate) is not suited for parenteral injection, which is necessary in the diagnosis and surgical management of pheochromocytoma. However, phentolamine hydrochloride is useful by the oral route for the control and prevention of blood pressure increases in patients with pheochromocytoma until surgical removal can be undertaken. For parenteral use and dosage of the drug, see the monograph on phentolamine methanesulfonate.

Phentolamine hydrochloride is relatively nontoxic, but oral administration of the drug may produce untoward side effects, such as tachycardia, orthostatic hypotension, nasal stuffiness and gastrointestinal disturbances, such as nausea, vomiting, and diarrhea.



Because of tachycardia, most patients do not tolerate the dosage required for sustained therapy of chronic hypertensive vascular disease. Withdrawal of medication is not always necessary, and, when it is employed in other conditions, a reduction in dosage frequently is followed by a disappearance of untoward symptoms.

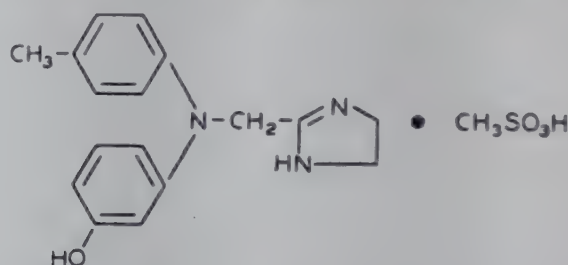
**Dosage.**—Phentolamine hydrochloride is administered orally. The usual adult dose is 50 mg. four to six times daily. Larger doses, as high as 100 mg., four to six times daily, may be necessary, especially in severer cases of peripheral vascular disease and hypertension. In children, the usual dosage is 25 mg. four to six times daily.

CIBA PHARMACEUTICAL PRODUCTS, INC.

Tablets Regitine Hydrochloride: 50 mg.

U. S. patent 2,503,059.

**PHENTOLAMINE METHANESULFONATE.**—Regitine Methanesulfonate (CIBA).—2- $\{[N-(m\text{-Hydroxyphenyl})-p\text{-toluidino}]methyl\}$ -2-imidazoline methanesulfonate.—The structural formula of phentolamine methanesulfonate may be represented as follows:



**Physical Properties.**—Phentolamine methanesulfonate is a white, odorless, bitter powder. It is freely soluble in water, very slightly soluble in acetone and practically insoluble in ethyl acetate. The amounts that dissolve in the following solvents to form 100 ml. of solution are: 6.8 Gm. in alcohol and 0.15 Gm. in chloroform. Phentolamine methanesulfonate is stable when protected from moisture. The pH of the 1 per cent solution is 4.5 to 5.5.

**Actions and Uses.**—Phentolamine methanesulfonate, a readily water-soluble salt of the adrenergic blocking agent phentolamine base, exhibits adrenolytic and sympatholytic effects. The methanesulfonate salt is used for parenteral injection in the diagnosis and surgical management of hypertension caused by pheochromocytoma, a tumor that characteristically gives rise to excessive circulating epinephrine and/or levarterenol (*l*-norepinephrine). Phentolamine, as the hydrochloride salt, is administered orally to control blood pressure increases in patients with pheochromocytoma until surgical removal can be undertaken. For other uses and the dosage of the orally administered hydrochloride salt, see the monograph on phentolamine hydrochloride.

Phentolamine effectively blocks the pressor activity of epinephrine and levarterenol for longer periods and in smaller amounts than does piperoxan. Therefore, phentolamine methanesulfonate

is considered more useful and less toxic than piperoxan as a diagnostic agent to exclude the presence of pheochromocytoma as a cause of paroxysmal or persistent hypertension. On the other hand, piperoxan is less likely to cause a misleading drop in blood pressure in ordinary cases of hypertension. It should, therefore, be employed as a confirmatory test when interpretation of the results is in doubt.

The use of phentolamine methanesulfonate as a diagnostic test for pheochromocytoma is based on its adrenolytic effect in producing a fall in blood pressure during a "typical" paroxysmal hypertensive episode. However, it is also indicated diagnostically in the presence of persistent chronic hypertension, especially when the hypertension is associated with a high basal metabolic rate, hyperglycemia and tachycardia, and in sudden severe hypertension in a normotensive or hypertensive patient during anesthesia or operative procedure and in hypertension in children or young adults, especially in the absence of severe renal disease. During the normotensive phase, that is, when the pheochromocytoma is not discharging sufficient epinephrine or levarterenol to elevate the blood pressure or to sustain an elevation, and in essential hypertension coexisting with a pheochromocytoma, repeated testing may be necessary to rule out "false negative" interpretation of a slight fall in blood pressure following administration of phentolamine.

A "false positive" drop in pressure may occur in patients with uremia and in those who have received sedatives prior to the test with phentolamine. Therefore, the test should be performed in the absence of sedation (or any anodyne) for at least 24 hours preceding. Basal blood pressure is first determined following a period of rest in the supine position, and the injection of the agent is delayed after introduction of the needle to allow the hypertensive effect of needle pain to subside.

The duration of the blood pressure response to phentolamine is influenced by the route of injection. Moderate or slight tachycardia is the only undesirable side effect of the test so far associated with intramuscular injection of the recommended dose. Given intravenously, the same dose has caused tachycardia with angina and, in rare instances, weakness, dizziness, or flushing, none of which have been considered serious. The diagnostic and therapeutic use of phentolamine methanesulfonate in pheochromocytoma is considered to be relatively safe and free from alarming reactions.

**Dosage.**—Phentolamine methanesulfonate is employed in permanently stable, lyophilized form for preparation of a fresh aqueous solution for administration by intramuscular or intravenous injection. In solution, phentolamine salts are stable for only about 6 months. For adults, the intramuscular or intravenous test dose is 5 mg. in 1 cc. of distilled water for injection; in children, an intramuscular dose of 3 mg. or an intravenous dose of 1 mg. is usually adequate. A typical positive response is characterized by an immediate drop in systolic and diastolic blood pressure. The maximum depressor effect is usually obtained within 2 minutes after intravenous injection and within 20 minutes after intramuscular injection. Generally, the systolic fall is approximately 60 mm. Hg, with



the diastolic fall exceeding 25 mm. Hg, but the degree of response may be somewhat less in some patients. After intramuscular injection, the reduction usually persists for some 30 minutes and gradually returns to previous levels within 3 to 4 hours. After intravenous administration, the blood pressure usually returns to previous levels within 10 to 15 minutes and occasionally within  $2\frac{1}{2}$  minutes. Negative responses are recorded when there is no change in blood pressure, a slight or moderate rise in blood pressure or only a slight lowering of blood pressure. The intravenous route should be employed if it is necessary to repeat the test to rule out false reactions.

In the control of blood pressure during surgical management of pheochromocytoma, the preoperative adult dose is 5 mg., intramuscularly or intravenously, 1 to 2 hours before the operation. This is repeated, if necessary, to prevent a paroxysm caused by anesthesia or emotional stress. For children, the preoperative dose is 3 mg. intramuscularly or 1 mg. intravenously. During operation, an intravenous dose of 5 mg. for adults or 1 mg. for children, repeated if necessary, may be given whenever blood pressure begins to rise as a result of stress or of manipulation of the tumor.

CIBA PHARMACEUTICAL PRODUCTS, INC.

**Lyophilized Regitine Methanesulfonate:** 5 mg. ampuls. Each ampul contains 5 mg. of phentolamine methanesulfonate. Packaged with 1 cc. vial of water for injection.

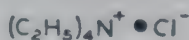
U. S. patent 2,503,059.

**PIPEROXAN HYDROCHLORIDE.**—See the monograph in the chapter on diagnostic aids.

### Agents with Both a Parasympatholytic and Sympatholytic Action

**HEXAMETHONIUM BROMIDE and HEXAMETHONIUM CHLORIDE.**—See the monographs in the chapter on cardiovascular agents.

**TETRAETHYLAMMONIUM CHLORIDE.** — Etamon Chloride (PARKE, DAVIS).—Tetraethylammonium chloride is made in the form of a 50 per cent solution in water. From this solution, the dosage forms are prepared. The structural formula of tetraethylammonium chloride may be represented as follows:



**Physical Properties.**—Tetraethylammonium chloride, isolated by evaporating the 50 per cent solution in a vacuum, is an extremely hygroscopic, odorless, white solid. It is very soluble in water and in alcohol, freely soluble in chloroform and practically insoluble in benzene and in ether. The pH of the 50 per cent solution is 5.8 to 6.5.

**Actions and Uses.**—Tetraethylammonium chloride is a quaternary ammonium compound belonging to a class of drugs which, like



nicotine and curare, act as generalized ganglionic blocking agents. The drug partially blocks transmission of motor nerve impulses through the ganglia of both the sympathetic and parasympathetic divisions of the autonomic nervous system. Its action is not adrenolytic and is interrupted by neostigmine. The blocking of sympathetic stimuli associated with vasospasm usually results in an increased blood supply to the affected region, accompanied by reduction in arterial pressure resulting from vasodilation. The simultaneous interference with the transmission of parasympathetic impulses produces loss of ocular accommodation, cessation or decrease of motility of the gastro-intestinal tract and alteration of urinary bladder function.

Tetraethylammonium chloride is of limited clinical usefulness as a therapeutic and diagnostic agent in the management of peripheral vascular diseases and other conditions involving vascular dysfunction. It has been employed successfully in the therapy of thromboangiitis obliterans (Buerger's disease), arteriosclerosis obliterans and various causalgias, including reflex dystrophy, herpes zoster, thrombophlebitis, Raynaud's disease, acrocyanosis, trench-foot and immersion foot. It may be employed diagnostically in acrovacular conditions to estimate the contribution of sympathetic stimuli in the maintenance of vasospasm.

Tetraethylammonium chloride promptly lowers blood pressure in both normal and hypertensive patients. Peripheral circulatory collapse has followed its use. Patients occasionally also experience dyspnea with hyperventilation, weakness, fatigue, lightheadedness, slowing of speech, dulling of the sensorium, difficulty in muscle movement which is not associated with impairment of the deep reflexes, dryness of the mouth and loss of ocular accommodation. The drug should be employed with caution in patients with severe hypertension, particularly in the presence of poor renal function or high diastolic pressure. Repeated administration should be avoided in the presence of impaired renal excretion. Tetraethylammonium chloride is not suitable for the treatment of hypertension because its hypotensive effect is not sustained. It should not be used in patients with recent coronary thrombosis and should be used with caution in all elderly patients and those with arteriosclerosis because they often experience unusual decrease in blood pressure with diminution in blood flow through the extremities.

**Dosage.**—Tetraethylammonium chloride is administered by intravenous or intramuscular injection. Intramuscular injection produces local tenderness and burning. Subcutaneous injection produces considerable local irritation, and oral administration is ineffective.

The intravenous dose is 2 to 5 cc. of a solution representing 0.2 to 0.5 Gm. (not to exceed 7 mg. per kilogram of body weight). The frequency of injection depends on the duration of the relief of symptoms. The effectiveness of the dose can be judged properly only on the basis of three or more injections. Injections may be given once or twice daily for several weeks in exceptional cases. The effects of the drug appear almost immediately following intravenous administration and postural hypotension lasts from

several minutes to 1 hour. Patients should be kept recumbent for at least 1 hour after intravenous injection.

The intramuscular dose is 10 to 12 cc. (5 to 6 cc. in each buttock) of the same concentration as that used intravenously, representing 1 to 1.2 Gm. (not to exceed 20 mg. per kilogram of body weight). This maintains an effective sympathetic block for 6 to 36 hours in hospitalized patients. Continuation of the autonomic blockade for longer than 36 hours usually causes considerable distress. The addition of 1 cc. of 2 per cent procaine hydrochloride solution to the dose of tetraethylammonium chloride decreases the discomfort caused by intramuscular injection.

Peripheral circulatory collapse should be treated by artificial respiration and/or injection of epinephrine hydrochloride solution 1:1,000. Intravenous administration of 0.5 to 1 mg. of neostigmine methylsulfate in solution antagonizes the blocking action of tetraethylammonium chloride and promotes rapid recovery from the postural hypotension.

PARKE, DAVIS & COMPANY

**Solution Etamon Chloride 10%:** 20 cc. Steri-Vials. A solution containing 0.1 Gm. of tetraethylammonium chloride in each cubic centimeter. Preserved with 0.005 per cent benzethonium chloride.

U. S. trademark 432,476.

## SYMPATHOMIMETIC AGENTS

Sympathomimetic agents are broadly defined as those drugs that induce bodily responses which imitate the effects of impulses conveyed by adrenergic postganglionic fibers of the sympathetic nervous system. Most of these agents are aromatic compounds, and their similarity of action is explained by a similarity of chemical structure in that the benzene nucleus which constitutes the aromatic portion of the molecule is separated from an amino nitrogen atom by two carbon atoms of the aliphatic portion of the molecule. Certain capabilities for substitution in either the aromatic or aliphatic portions have led to the synthesis of a large number of sympathomimetic amines, which, while retaining sympathomimetic activity, exhibit new properties that are chemically useful. Chemically dissimilar compounds that possess sympathomimetic activity have also been developed.

Sympathomimetic agents can be grouped according to their aliphatic portions. Thus epinephrine and kephrine have identical aromatic portions; ephedrine and phenylpropanolamine, and tyramine and hydroxyamphetamine are similarly paired. Again, epinephrine and phenylephrine have identical aliphatic portions; amphetamine and hydroxyamphetamine are similarly paired. Amphetamine, hydroxyamphetamine and tuaminoheptane possess, as a common feature, an aliphatic 3-carbon chain with an amino group attached to the middle carbon atom; their differences lie in the rest of the molecules. Amphetamine is distinguished by a simple benzene ring, while hydroxyamphetamine has a benzene ring with



one OH group added; in place of the benzene ring, tuaminoheptane has a butyl group. When stereoisomeric forms of sympathomimetic agents exist the dextrorotatory form may differ greatly in activity from the levorotatory form.

Ephedrine, amphetamine and phenylephrine differ from epinephrine in that their excitatory actions are only diminished, and not reversed, by the sympatholytic agents (ergotoxine, dihydroergotamine, dibenamine, priscoline), and cocaine (possessing certain sympathomimetic properties) does not potentiate their effects. Most of the pharmacologic differences between ephedrine and epinephrine are well known, but may be repeated to illustrate differences between other members of this class of autonomic drugs. Ephedrine, in contrast to epinephrine, is effective orally, has more prolonged action, produces less arteriolar constrictor effect, fails to act if given too frequently (tachyphylaxis) and affects skeletal muscle. The central stimulatory effects of ephedrine and amphetamine are disadvantages when only peripheral effects are desired, but render them useful under other circumstances.

With certain exceptions, sympathomimetic drugs produce mydriasis and/or relaxation of the ciliary muscle; decreased tone of bronchioles, stomach, intestine, bladder and ureter; contraction of smooth muscle sphincters, the splenic capsule and pregnant uterus; constriction of blood vessels other than coronary; inhibition of the secretion of certain glands; and increased cardiac rate and output. Their principal therapeutic use is based on their most prominent actions; namely, those on the heart, blood vessels and certain smooth muscles.

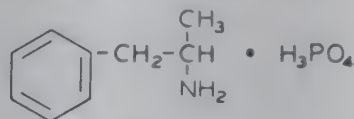
The cardiovascular response to a sympathomimetic amine is frequently modified by the presence of a previous dose of the same, or another amine. The pressor response may be increased, decreased or inverted to a depressor action. For instance, phenylpropylmethyamine pressor action is inverted to depressor action by the presence of hydroxyamphetamine, but not by other amines. Epinephrine, although the most potent pressor amine, dilates capillaries, perhaps accounting for the hypotension seen to follow its transient vasoconstriction of the arterioles. Reversal of its constrictor action occurs when its use is preceded by administration of sympatholytic agents.

Ventricular arrhythmias, even fibrillation, may follow the use of epinephrine, particularly during surgical anesthesia, so its use may be dangerous in such circumstances. In patients with medical or surgical shock, it may aggravate the underlying cause. It should not be given in the presence of emphysematous bronchial asthma. Pressor effects of any of these compounds are to be avoided in hyperthyroidism and hypertensive heart disease.

Milder side reactions of anxiety, tension, restlessness, insomnia, tremor, weakness and palpitation may also interfere with the clinical use of these compounds. In this group the claimed advantage of one compound over another depends largely on the purpose for which it is employed; an undesirable side effect in one instance becomes a useful therapeutic action in another.



**AMPHETAMINE PHOSPHATE.**—Raphetamine Phosphate (STRAS-ENBURGH).— $\alpha$ -Methylphenethylamine phosphate.—Racemic Monobasic Amphetamine Phosphate.—The structural formula of amphetamine phosphate may be represented as follows:



**Physical Properties.**—Amphetamine phosphate is a white, odorless powder with a bitter taste. It sinters at about  $150^\circ$ , becomes an amorphous mass as heating is continued and decomposes at about  $300^\circ$ . It is freely soluble in water, slightly soluble in alcohol and practically insoluble in benzene, chloroform and ether. The pH of a 10 per cent solution is about 4.6.

**Actions and Uses.**—Amphetamine phosphate shares the actions and uses of amphetamine sulfate. Its one advantage, greater solubility, is significant only in the preparation of solutions for injection. For the indications for its use see the monograph on amphetamine sulfate.

**Dosage.**—Doses of amphetamine phosphate approximately 20 per cent greater by weight than those recommended for amphetamine sulfate provide the same amount of the base. Because the average oral dose seldom exceeds 10 mg., the difference between the prescribed amount of the phosphate and sulfate is likely to be clinically undetectable. Theoretically, 12 mg. of amphetamine phosphate represents the approximate equivalent of 10 mg. of amphetamine sulfate. As an analeptic, the drug is administered intravenously or intramuscularly in doses of 20 to 50 mg. every 30 to 60 minutes until consciousness is restored. The same precautions and contraindications must be observed as in the case of other sympathomimetic amine compounds.

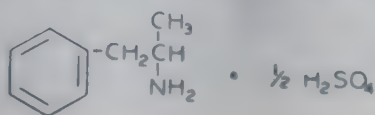
R. J. STRASENBURGH COMPANY .

**Elixir Raphetamine Phosphate:** 473 cc. and 3.78 liter bottles. A flavored alcohol solution containing 1.25 mg. of amphetamine phosphate in each cubic centimeter.

**Solution Raphetamine Phosphate 1%:** 10 cc. vials. A solution containing 10 mg. of amphetamine phosphate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Tablets Raphetamine Phosphate:** 5 mg.

**AMPHETAMINE SULFATE-U.S.P.**—Benzedrine Sulfate (SMITH, KLINE & FRENCH).— $\alpha$ -Methylphenethylamine sulfate.—“Amphetamine Sulfate, dried at  $105^\circ$  for 2 hours, contains not less than 98 per cent of  $(\text{C}_9\text{H}_{13}\text{N})_2\cdot\text{H}_2\text{SO}_4$ .” *U.S.P.* The structural formula of amphetamine sulfate may be represented as follows:



**Physical Properties.**—Amphetamine sulfate occurs as a white, odorless powder which is freely soluble in water and slightly soluble in alcohol. Its aqueous solution is neutral to litmus.

**Actions and Uses.**—Amphetamine sulfate has been widely employed in the treatment of narcolepsy, in controlling the oculogyric crises and various other manifestations of postencephalitic parkinsonism and as an adjunct in the treatment of alcoholism, but its most extensive therapeutic application has been in the treatment of certain depressive conditions, especially those characterized by apathy and psychomotor retardation.

The drug's stimulating effect on the central nervous system renders it effective in the symptomatic treatment of many mild psychogenic depressive states, particularly those attending childbirth, persistent pain, chronic organic disease, menopause and old age; or associated with morning tiredness, chronic fatigue, prolonged post-operative recovery or psychogenic bodily ailments. Results in psychoneuroses are variable, however. In these mild psychogenic disorders the use of the drug should be subordinated to treatment of the underlying causes.

Amphetamine sulfate may also be of value to a lesser extent, in symptomatic treatment of more severe depressions accompanying certain major psychopathic conditions. While the drug is useful in the treatment of depressive states, it does not alter the course of the underlying psychosis in major psychopathic conditions. Obviously, severely depressed psychopathic patients should be institutionalized.

Again due to its ameliorative influence on mental depression, amphetamine is useful as an adjunct in the treatment of alcoholism. In chronic alcoholism, especially, it may provide a desirable means of interrupting the vicious alcoholic cycle, thus permitting the institution of more fundamental psychotherapeutic measures. In acute alcoholism, with or without accompanying psychosis, the drug may occasionally be useful in combating pathologic intoxication. (In alcoholic psychoses best results are reported where the psychosis is of recent origin.)

In addition, the drug is effective in the symptomatic treatment of orthostatic hypotension. It is not recommended for use in spastic colitis or pyloric spasm.

In suitable cases, amphetamine sulfate is useful as an appetite-depressant for obtaining weight reduction in the management of obesity. It has been found to allay the sensation of hunger, although there is still some doubt as to the mechanism of this action. It may assist some individuals in adhering to a strict dietary regimen and is especially valuable in those patients in whom over-eating is a response to a depressive state.

The use of amphetamine sulfate to alleviate sleepiness and fatigue by persons not under medical control is to be condemned. The dangers lie in the elimination of the warning signal of fatigue in individuals who are overdoing, the possibility of habit formation on continued use and undesirable circulatory effects. Collapse has occurred in some such cases. Except when administered under the strict supervision of the physician, its use is not recommended for



developing a sense of exhilaration, increased energy and capacity for work; nor as a "pick-me-up" following temporary alcoholic overindulgence.

Because of the pharmacologic nature of amphetamine, its administration may produce overstimulation, restlessness, sleeplessness and gastro-intestinal disturbance; overdosage may be followed by chills, collapse and syncope. Amphetamine should be administered with caution in the presence of hypertension or cardiovascular disease. It is contraindicated in patients manifesting anxiety, hyperexcitability, or undue restlessness. Deleterious effects may be produced from habituation to the drug, although cases of habit formation are rare.

**Dosage.**—Since effective dosage varies considerably with the individual patient and with the condition being treated, initial doses should be small (5 mg. or less), and should be increased gradually until a definite effect appears. The use of a small test dose is particularly important in the treatment of depressive states. In most cases, it is desirable to administer the drug in divided doses. To avoid interference with sleep, the final daily dose should ordinarily be given not later than 4 P.M. The usual therapeutic dose is from 5 to 30 mg., though larger doses are occasionally given.

To depress the appetite in overweight, doses of 5 to 10 mg. three times daily, preferably administered one-half to one hour before each meal, are usually sufficient. The dosage should be adjusted to individual needs and should be the minimum necessary to produce the desired reduction of appetite. In no instance should it exceed 30 mg. daily. To minimize the possibility of initial over-stimulation the physician should begin treatment with smaller doses, increasing them gradually until optimal results are achieved.

A capsule containing fractionally enteric-coated pellets of the drug, designed to permit sustained release of medication, can be administered orally in doses of 15 mg. to provide continuous action for 8 to 12 hours. In patients with hypermotility of the intestinal tract, the duration of the effect occasionally may be shortened so that the usual tablet form may be more effective in such cases.

#### BIORGANIC LABORATORIES, INC.

**Powder Amphetamine Sulfate:** 100 Gm., 1 Kg. and bulk packages for compounding use.

#### GOLD LEAF PHARMACAL COMPANY, INC.

**Tablets Amphetamine Sulfate:** 5 mg. and 10 mg.

#### LINCOLN LABORATORIES, INC.

**Tablets Amphetamine Sulfate:** 10 mg.

#### PHYSICIANS' DRUG & SUPPLY COMPANY

**Tablets Amphetamine Sulfate:** 5 mg. and 10 mg.

#### PREMO PHARMACEUTICAL LABORATORIES, INC.

**Tablets Amphetamine Sulfate:** 10 mg.



SMITH, KLINE & FRENCH LABORATORIES

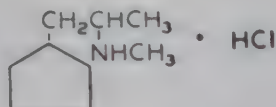
Spansule Sustained Release Capsules Benzedrine Sulfate: 15 mg.

Powder Benzedrine Sulfate: 2.5 Gm. bottles.

Tablets Benzedrine Sulfate: 5 mg. and 10 mg.

U. S. trademarks 337,407 and 562,210.

**CYCLOPENTAMINE HYDROCHLORIDE.**—**Clopene Hydrochloride** (LILLY). — N,α-Dimethylcyclopentaneethylamine hydrochloride.—1-Cyclopentyl-2-methylaminopropane hydrochloride.—The structural formula of cyclopentamine hydrochloride may be represented as follows:



**Physical Properties.**—Cyclopentamine hydrochloride is a white, odorless, crystalline powder with a mild characteristic odor and a bitter taste. It melts between 113.0° and 116.0°. One part of cyclopentamine hydrochloride is soluble in 1.0 part of water, in 1.8 parts of alcohol, in 23.8 parts of benzene and in 1.3 parts of chloroform, and is slightly soluble in ether. The pH of a 1 per cent solution is about 6.2.

**Actions and Uses.**—Cyclopentamine hydrochloride has the actions and uses of sympathomimetic amines. It produces systemic pressor and local vasoconstrictor effects similar to those of ephedrine; but, unlike ephedrine, produces only slight cerebral excitation. Given orally it is more effective than ephedrine.

The drug is administered by injection as an adjunct to other measures for maintaining blood pressure in operative procedures and in types of cardiovascular collapse where sympathomimetic drugs are not contraindicated. It is also useful by topical application for the temporary relief of nasal congestion. Its local vasoconstrictor action does not appreciably interfere with ciliary movements.

Like other sympathomimetic agents, cyclopentamine hydrochloride should not be injected in patients with hyperthyroidism, and should be used with caution in patients with hypertension. Too frequent topical application should also be avoided to prevent such side effects as increased blood pressure, nervousness, nausea and dizziness, particularly in patients susceptible to vasoconstrictor agents.

**Dosage.**—As a nasal decongestant, a 0.5 per cent solution is applied topically by means of dropper, spray or tampon. Drops should be instilled with the head in the lateral head-low position; when stinging is encountered the solution may be diluted with isotonic sodium chloride solution.

A 1 per cent solution may be employed for office procedures or prescribed for use by patients who do not obtain adequate shrinkage with the 0.5 per cent concentration of the drug.

As a pressor agent to maintain blood pressure during spinal anesthesia or surgery, a dose of 25 mg. in 1 cc. of solution is recommended. It is injected intramuscularly just prior to administration of the anesthetic, with subsequent fractional doses as needed. To combat a rapid fall in blood pressure the drug may be administered intravenously, but by this route the drug must be injected very slowly and in doses not exceeding 5 to 10 mg. in order that the full effect of each dose may be determined.

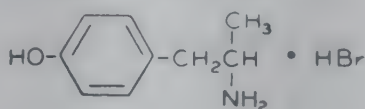
#### ELI LILLY & COMPANY

**Solution Clopane Hydrochloride:** 1 cc. ampuls. A solution containing 25 mg. of cyclopentamine hydrochloride in each cubic centimeter.

**Topical Solution Clopane Hydrochloride 0.5%:** 30 cc., 475 cc. and 3.78 liter bottles. An isotonic solution containing 5 mg. of cyclopentamine hydrochloride in each cubic centimeter. Preserved with phenylmercuric nitrate 1:50,000.

**Solution Clopane Hydrochloride 1%:** 30 cc. and 475 cc. bottles. An isotonic solution containing 10 mg. of cyclopentamine hydrochloride in each cubic centimeter. Preserved with phenylmercuric nitrate 1:50,000.

**HYDROXYAMPHETAMINE HYDROBROMIDE.**—**Paredrine Hydrobromide** (SMITH, KLINE & FRENCH).—*p*-(2-Aminopropyl)-phenol hydrobromide. — *p*-Hydroxy- $\alpha$ -methylphenethylamine hydrobromide.—The structural formula of hydroxyamphetamine hydrobromide may be represented as follows:



**Physical Properties.**—Hydroxyamphetamine hydrobromide is a white, crystalline solid with a faint odor. It melts between 189° and 192°. It is very soluble in water, freely soluble in alcohol and practically insoluble in benzene and ether. A 2 per cent solution of hydroxyamphetamine hydrobromide has a pH between 4.5 and 5.5.

**Actions and Uses.**—Hydroxyamphetamine hydrobromide shares the general properties of other sympathomimetic amines. Animal studies indicate it to be somewhat less toxic than epinephrine and amphetamine. It produces little or no ephedrinelike central stimulation. Its principal therapeutic usefulness is therefore dependent on its peripheral effects. It is employed in solution for topical application to produce shrinkage of the nasal mucosa. For this purpose, at equal dosage levels, it is about twice as effective as ephedrine, in terms both of quickness and duration of action, and also less irritating. A 1 per cent solution of the drug instilled in the eye produces mydriasis suitable for ophthalmoscopic examination and, as an adjuvant to atropine and homatropine, helps in the induction of cycloplegia for refraction of adults and children, also promoting



a rapid return of accommodation. By injection or by oral administration, the drug produces cardiovascular and intestinal effects similar, though not identical, to other sympathomimetic agents.

**Dosage.**—Hydroxyamphetamine hydrobromide is used in 1 per cent solution for topical application by instillation, tamponage or by atomized spray into the nostrils for shrinking of the nasal mucosa. The administration of 2 to 5 drops four to five times daily is usually sufficient for instillation. For sinus irrigation or displacement, the 1 per cent solution should be diluted with three parts of isotonic sodium chloride solution to make a 0.25 per cent solution of the drug.

A 1 per cent solution is also employed for instillation in the eye. For mydriasis, 1 or 2 drops are placed in the conjunctival sac. As an adjuvant for cycloplegia, 1 or 2 drops are instilled shortly after initial induction with 4 or 5 per cent solution of homatropine hydrobromide for adults, or a 1 per cent solution of atropine sulfate for children. Maximum cycloplegia is produced in 60 minutes. Full recovery in adults usually occurs the day after examination and, in children, the accommodative disability is reduced to 3 to 5 days.

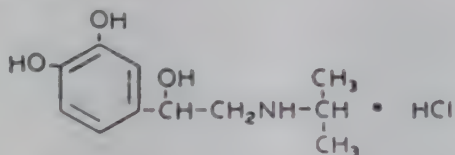
#### SMITH, KLINE & FRENCH LABORATORIES

**Aqueous Solution Paredrine Hydrobromide:** 30 cc. and 360 cc. bottles. An aqueous solution containing 10 mg. of hydroxyamphetamine hydrobromide in each cubic centimeter. Preserved with thimerosal 1:100,000.

**Ophthalmic Solution Paredrine Hydrobromide:** 15 cc. dropper bottles. An aqueous solution containing 10 mg. of hydroxyamphetamine hydrobromide in each cubic centimeter. Made isotonic with 20 mg. of boric acid in each cubic centimeter. Preserved with thimerosal 1:50,000.

U. S. patent 2,181,845. U. S. trademark 344,351.

**ISOPROPYLARTERENOL HYDROCHLORIDE.**—Aludrine Hydrochloride (LILLY).—Isuprel Hydrochloride (WINTHROP-STEARNES).— $\alpha$ -(Isopropylaminomethyl)protocatechuyl alcohol hydrochloride.—1-(3',4'-Dihydroxyphenyl)-2-isopropylaminoethanol hydrochloride.—The structural formula of isopropylarterenol hydrochloride may be represented as follows:



**Physical Properties.**—Isopropylarterenol hydrochloride is a white, odorless, slightly bitter, nonhygroscopic, crystalline solid. It melts between 166 and 172°. It is freely soluble in water, soluble in alcohol and very slightly soluble in benzene and ether. A 1 per cent solution of isopropylarterenol hydrochloride is clear and colorless,



and has a pH between 4.5 and 5.5. Aqueous solutions of isopropylarterenol hydrochloride become pink upon standing.

**Actions and Uses.**—Isopropylarterenol is a sympathomimetic amine closely related in its actions to epinephrine and levarterenol. There are certain important differences, however. The action on the smooth muscle of blood vessels is much less pronounced than with epinephrine or arterenol, and in some experimental animals, a fall in blood pressure occurs. In man, the effects on blood pressure from therapeutic doses are usually unimportant, a slight rise in systolic and a slight fall in diastolic pressure occasionally being noted. Larger doses may cause considerable peripheral vasodilatation and in some individuals diastolic pressure may fall without a corresponding fall in systolic pressure. Such effects are usually fleeting.

Isopropylarterenol is a powerful cardiac accelerator and moderate dosage may produce an extreme tachycardia. The resultant cardiac insufficiency is characterized by precordial distress, palpitation, shock and electrocardiographic changes which suggest coronary insufficiency.

In some patients, isopropylarterenol may cause dizziness, nausea, tremors and excitement. These reactions are similar to those produced by other sympathomimetic agents.

The principal therapeutic effects of isopropylarterenol occur in the bronchi. The drug will overcome histamine-induced asthma in guinea pigs as well as protect against anaphylactic shock. In animals, the effects on the bronchi are quantitatively greater than those observed following similar doses of epinephrine.

When administered sublingually or by oral inhalation, isopropylarterenol salts are effective in the treatment of mild and moderately severe asthma. Following oral inhalation the drug tends to liquefy tenacious mucus, thus exerting a mild expectorant action. The drug is effective in epinephrine-fast patients. Powder preparations of this drug for inhalation produce greater systemic effects than do aerosol preparations. Frequent side reactions are common with this form of therapy.

**Dosage.**—Sublingually, 10 to 15 mg. of isopropylarterenol hydrochloride is administered not oftener than every 3 to 4 hours or more than three times daily. By oral inhalation, in the treatment of acute asthmatic attacks, not more than 0.5 cc. of a 1:200 solution or 0.1 to 0.3 cc. of a 1:100 solution may be nebulized for each dose.

For mild or moderately acute attacks of asthma a 10 per cent isopropylarterenol powder may be inhaled from a suitable device. Not more than two to four normal inhalations should be taken and the dose should not be repeated more frequently than every 15 to 30 minutes. In severe attacks the 25 per cent powder may be used in the same manner, but it produces more frequent and severe side effects than the less concentrated powder.

Isopropylarterenol should not be given subcutaneously or intravenously because of the profound myocardial stimulation produced by small doses administered by these routes. Likewise, the drug

should not be administered with epinephrine, although the two drugs may be used alternately.

CHEMO PURO MANUFACTURING CORPORATION

**Powder Isopropylarterenol Hydrochloride:** Bulk; for manufacturing use.

ELI LILLY & COMPANY

**Sublingual Tablets Aludrine Hydrochloride:** 5 mg. and 10 mg.

WINTHROP-STEARNs, INC.

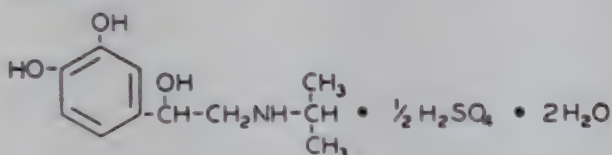
**Inhalant Solution Isuprel Hydrochloride 1:100:** 10 cc. bottles. A solution containing 10 mg. of isopropylarterenol hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol and 0.3 per cent sodium bisulfite.

**Inhalant Solution Isuprel Hydrochloride 1:200:** 10 cc. and 50 cc. bottles. A solution containing 5 mg. of isopropylarterenol hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol and 0.3 per cent sodium bisulfite.

**Glossets Isuprel Hydrochloride:** 10 mg. and 15 mg. Each tablet contains 10 mg. and 15 mg. of isopropylarterenol hydrochloride. Preserved with 2 mg. of sodium bisulfite.

Licensed under U. S. patent 2,308,232. U. S. trademark 436,982.

**ISOPROPYLARTERENOL SULFATE.**—Isonorin Sulfate (CARROLL DUNHAM SMITH).—Norisodrine Sulfate (ABBOTT).— $\alpha$ -(Isopropylaminomethyl)protocatechuyl alcohol sulfate dihydrate.—1-(3',4'-Dihydroxyphenyl)-2-isopropylaminoethanol sulfate dihydrate.—The structural formula of isopropylarterenol sulfate may be represented as follows:



**Physical Properties.**—Isopropylarterenol sulfate is a white, odorless, slightly bitter, hygroscopic, crystalline solid. It melts at about 128° with decomposition. It is freely soluble in water, slightly soluble in alcohol and very slightly soluble in benzene and ether. A 1 per cent solution of isopropylarterenol sulfate is clear and colorless, and has a pH between 3.5 and 4.5. Aqueous solutions of isopropylarterenol sulfate become pink upon standing.

**Actions, Uses and Dosage.**—See the monograph on isopropylarterenol hydrochloride.

ABBOTT LABORATORIES

**Powder (Inhalant) Norisodrine Sulfate 10% and 25%:** 10 mg. and 25 mg. Aerohalor Cartridges, respectively.

U. S. trademark 529,568 (Aerohalor Cartridges).



**Solution (Inhalant) Norisodrine Sulfate 1:100:** 10 cc. bottles. A solution containing 10 mg. of isopropylarterenol sulfate in each cubic centimeter. Preserved with 0.1 per cent sodium metabisulfite and 0.15 per cent methylparaben.

U. S. trademark 502,747.

**CHEMO PURO MANUFACTURING CORPORATION**

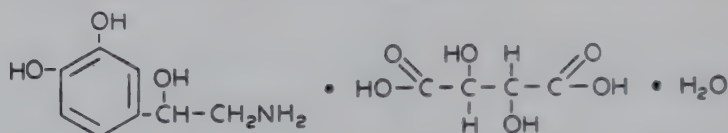
**Powder Isopropylarterenol Sulfate:** Bulk; for manufacturing use.

**CARROLL DUNHAM SMITH PHARMACAL COMPANY**

**Inhalant Solution Isonorin Sulfate 1:200:** 15 cc. vials. A solution containing 5 mg. of isopropylarterenol sulfate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium metabisulfite.

**Sublingual Tablets Isonorin Sulfate:** 10 mg. Each tablet contains 10 mg. of isopropylarterenol sulfate. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium metabisulfite.

**LEVARTERENOL BITARTRATE.**—Levophed Bitartrate (WINTHROP-STEARNES).—*l*- $\alpha$ -(Aminomethyl)-3,4-dihydroxybenzyl alcohol *d*-bitartrate monohydrate.—The structural formula of levarterenol bitartrate may be represented as follows:



**Physical Properties.**—Levarterenol bitartrate is a white, crystalline, odorless powder. It melts between 100 and 106°. It is freely soluble in water, slightly soluble in alcohol and insoluble in ether. The pH of a 0.1 per cent solution is between 3.0 and 4.0.

**Actions and Uses.**—Levarterenol bitartrate, a water-soluble salt of the levo isomer of the primary pressor amine, arterenol, differs chemically from epinephrine by the absence of a methyl group on the nitrogen atom. Its action differs clinically from that of epinephrine chiefly by its over-all vasoconstrictor influence, its marked slowing of the pulse rate of horizontal subjects, and the absence of a stimulant effect on cardiac output. Levarterenol bitartrate produces a rise in blood pressure because it functions as a sympathetic mediator of peripheral vasoconstriction, whereas epinephrine acts as an over-all vasodilator and induces hypertension only by increasing cardiac output. In this respect, arterenol is similar to synthetic pressor amines, such as phenylephrine, which are preferred to epinephrine in the treatment of hypotensive states caused by central vasomotor failure and peripheral circulatory collapse. Levarterenol bitartrate produces about two and one-half times the degree of vasodilatation on the coronary arteries that is produced by epinephrine. It may be administered to diabetic patients because its hyperglycemic effect is slight.

Levarterenol bitartrate is useful for the maintenance of blood



pressure in acute hypotensive states caused by surgical and non-surgical trauma, central vasomotor depression and hemorrhage. It should not be employed for ordinary shock in place of appropriate intravascular fluids, such as plasma, when the fall in blood pressure is primarily the result of decreased blood volume rather than impaired vasomotor activity.

Levarterenol bitartrate is reported to have a safety ratio (pressor activity to toxicity) that is four times greater than that of epinephrine. Because of this and its lesser effect on the heart, levarterenol bitartrate is considered to be better tolerated and relatively safer than epinephrine. Infusion of levarterenol bitartrate may produce a bradycardia, apparently of vagal origin, which is abolished by atropine. A few cases of transient headache and hypersensitivity have been observed following its use. Levarterenol bitartrate is contraindicated when cyclopropane anesthesia is employed because of the possibility of increasing the risk of ventricular fibrillation.

**Dosage.**—Levarterenol bitartrate is administered by intravenous infusion in either isotonic sodium chloride solution, 5 per cent dextrose solution, human plasma or whole blood. An amount sufficient to make a final dilution of 4 mcg. (base) per cubic centimeter is usually prepared by adding 4 cc. of a 0.2 per cent solution of levarterenol bitartrate (equivalent to 0.1 per cent of the base) to each 1,000 cc. of the fluid to be administered. This concentration should be given through a previously calibrated Murphy drip bulb which will permit an accurate estimation of the rate of flow in drops per minute. An initial dose of 1 to 2 mcg. of the base (0.25 to 0.5 cc. of the dilution) per 10 Kg. of body weight is given and its effect on the blood pressure carefully observed. The rate of flow then should be adjusted to maintain the desired tension. The average dose ranges from 2 to 4 mcg. of the base (0.5 to 1 cc. of the dilution) per minute.

The blood pressure should be checked every 2 minutes from the time the drug is started until the desired level is obtained and every 5 minutes thereafter to avoid overdosage and dangerous hypertension. The rate of infusion must be watched constantly and the patient should never be left unattended while receiving the drug. Since subcutaneous extravasation of the solution may produce tissue necrosis, the needle or plastic tubing should be advanced well into the vein and secured in place.

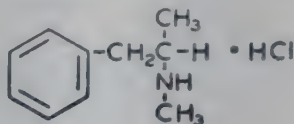
WINTHROP-STEARNs, INC.

**Solution Levophed Bitartrate 0.2%:** 4 cc. ampuls. An isotonic solution containing 2 mg. of levarterenol bitartrate in each cubic centimeter. Preserved with 0.2 per cent sodium bisulfite.

U. S. trademark 434,232.

**METHAMPHETAMINE HYDROCHLORIDE-U.S.P.**—Amphedroxyn Hydrochloride (LILLY).—Desoxyephedrine Hydrochloride (UPJOHN).—Desoxyn Hydrochloride (ABBOTT).—Dexoval Hydrochloride (VALE).—Doxyfed Hydrochloride (RAYMER).—Efroxine Hydrochloride (MALTBIÉ).—Norodin Hydrochloride (ENDO).—Semoxydrine

**Hydrochloride (MASSENGILL).—Syndrox Hydrochloride (MCNEIL).**—*d*-Desoxyephedrine hydrochloride.—*d*-N, $\alpha$ -Dimethylphenethylamine hydrochloride.—The structural formula of methamphetamine hydrochloride may be represented as follows:



**Physical Properties.**—Methamphetamine hydrochloride occurs as white crystals or as a white, crystalline powder. It is odorless, and its water solution is acid to litmus paper. One gram of methamphetamine hydrochloride dissolves in 2 cc. of water, 3 cc. of alcohol and 5 cc. of chloroform; it is very slightly soluble in absolute ether.

**Actions and Uses.**—The actions of methamphetamine hydrochloride differ from those of amphetamine sulfate only in degree. The central stimulant effects of methamphetamine hydrochloride may be slightly greater and the circulatory action slightly less than those of amphetamine.

Methamphetamine hydrochloride may be used in the treatment of narcolepsy, in controlling oculogyric crises and various other manifestations of postencephalitic parkinsonism, as an adjunct in the treatment of alcoholism and in the treatment of certain depressive conditions, especially those characterized by apathy and psychomotor retardation. The drug may be administered intravenously as a cerebral stimulant to facilitate psychotherapeutic interviews with psychotic or neurotic patients. In emergencies it is administered intravenously as a cardiovascular stimulant; in barbiturate poisoning and also in acute alcoholism it is used as an analeptic.

Methamphetamine hydrochloride has been used as an adjunct in the treatment of obesity. It depresses the motility of the gastrointestinal tract and allays the sensation of hunger. It may assist some patients adhere to a strict dietary regime and also help those who are overeating in response to a depressive state.

Solutions of the drug may be administered by injection to sustain or prevent a fall in blood pressure during intravenous barbiturate, spinal or regional block anesthesia.

Contraindications to the use of methamphetamine hydrochloride are hypertensive states, hyperthyroidism, insomnia, arteriosclerosis in the aged, nephritis, coronary disease and myocardial damage.

**Dosage.**—Orally: The initial dose of methamphetamine hydrochloride is 2.5 mg. daily; this may be increased to 2.5 to 5 mg. two or three times daily if necessary. To avoid insomnia, the drug should not be administered after 4 P.M.; excessive dosage may also interfere with normal rest. In the event of signs of toxicity—restlessness, sleeplessness, headache, vertigo, palpitation and arrhythmia—the drug should be discontinued and a sedative administered.



**Parenterally:** In emergencies a solution containing 10 to 15 mg. of methamphetamine hydrochloride may be administered slowly by intravenous injection. A second injection should follow only after 15 to 20 minutes or when the full effects of the first have been realized. For emergencies, the corresponding intramuscular dose is 15 to 30 mg. To sustain or prevent a fall in blood pressure during barbiturate, spinal or regional anesthesia, a dose of 20 mg. is administered subcutaneously immediately prior to induction, and repeated as necessary during the operative procedure. A dose of 15 to 20 mg. administered intravenously at a moderate rate is used to facilitate communication with psychiatric patients.

#### ABBOTT LABORATORIES

**Elixir Desoxyn Hydrochloride:** 473 cc. and 3.78 liter bottles. An elixir containing 0.66 mg. of methamphetamine hydrochloride in each cubic centimeter.

**Solution Desoxyn Hydrochloride:** 1 cc. ampuls. A solution containing 20 mg. of methamphetamine hydrochloride in each cubic centimeter.

**Tablets Desoxyn Hydrochloride:** 2.5 mg. and 5 mg.

U. S. trademark 434,257.

#### BIORGANIC LABORATORIES, INC.

**Powder Methamphetamine Hydrochloride:** Bulk; for compounding or manufacturing use.

#### ENDO PRODUCTS, INC.

**Powder Norodin Hydrochloride:** 1 Gm., 5 Gm. and 10 Gm. vials.

**Tablets Norodin Hydrochloride:** 2.5 mg. and 5 mg.

#### ELI LILLY & COMPANY

**Elixir Amphetroxyn Hydrochloride:** 473 cc. and 3.78 liter bottles. A solution containing 0.62 mg. of methamphetamine hydrochloride in each cubic centimeter.

**Tablets Amphetroxyn Hydrochloride:** 2.5 and 5 mg.

#### MALTBIE LABORATORIES, INC.

**Elixir Efroxine Hydrochloride:** 118.3 cc., 473 cc. and 3.78 liter bottles. An elixir containing 0.66 mg. of methamphetamine hydrochloride in each cubic centimeter.

**Tablets Efroxine Hydrochloride:** 5 mg.

U. S. trademark 547,887.

#### S. E. MASSENGILL COMPANY

**Tablets Semoxydrine Hydrochloride:** 2.5 mg., 5.0 mg. and 7.5 mg.

U. S. trademark 538,256.

#### MCNEIL LABORATORIES, INC.

**Elixir Syndrox Hydrochloride:** 473 cc. and 3.78 liter bottles. An



elixir containing 0.67 mg. of methamphetamine hydrochloride in each cubic centimeter.

**Tablets Syndrox Hydrochloride: 5 mg.**

U. S. trademark 529,491.

**RAYMER PHARMACAL COMPANY**

**Solution Doxyfed Hydrochloride:** 473 cc. and 3.78 liter bottles. A flavored aqueous solution containing 1.5 mg. of methamphetamine hydrochloride in each cubic centimeter.

**Tablets Doxyfed Hydrochloride:** 2.5 mg. and 5 mg.

**REXALL DRUG COMPANY**

**Tablets Methamphetamine Hydrochloride:** 2.5 mg. and 5 mg.

**THE UPJOHN COMPANY**

**Tablets Desoxyephedrine Hydrochloride: 5 mg.**

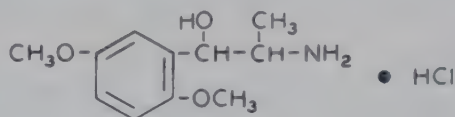
**THE VALE CHEMICAL COMPANY, INC.**

**Tablets Dexoval Hydrochloride:** 2.5 mg. and 5 mg.

**THE WARREN-TEED PRODUCTS COMPANY**

**Tablets Methamphetamine Hydrochloride: 5 mg.**

**METHOXAMINE HYDROCHLORIDE.**—**Vasoxyl Hydrochloride** (BURROUGHS WELLCOME).— $\alpha$ -(1-Aminoethyl)-2,5-dimethoxybenzyl alcohol.— $\beta$ -Hydroxy- $\beta$ -(2,5-dimethoxyphenyl)isopropylamine hydrochloride.—The structural formula of methoxamine hydrochloride may be represented as follows:



**Physical Properties.**—Methoxamine hydrochloride is a white, bitter, crystalline powder with a very slight odor; it melts at 212 to 216°. It is freely soluble in water and very slightly soluble in ether and ethyl acetate. In alcohol 8.8 Gm. dissolve to form 100 ml. of solution. The pH of the 2 per cent solution is 4.0 to 5.0.

**Actions and Uses.**—Methoxamine hydrochloride is a sympathomimetic amine compound which exhibits the vasopressor action (peripheral vasoconstriction) characteristic of other chemical agents of this class. Unlike the action of most pressor amines, the cardiac rate decreases as the blood pressure increases. This bradycardia, which is apparently caused by a carotid sinus reflex mediated by the vagus nerve, is abolished by atropine. Although the drug tends to slow the ventricular rate, it does not produce ventricular tachycardia, fibrillation or an increased sino-auricular rate nor does it increase the irritability of the cyclopropane-sensitized heart. Methoxamine also is free of cerebral-stimulating action. Tachyphylaxis has not been observed clinically.

Methoxamine hydrochloride is indicated primarily during surgery to maintain adequately or restore arterial blood pressure, especially in conjunction with spinal anesthesia, which tends to produce a fall in blood pressure. It is also useful as an adjunct in the treatment of hypotension associated with hemorrhage, trauma and surgery. Its adjunctive use is particularly indicated immediately prior to emergency operations in hypotensive patients who are poor surgical risks. It may be helpful in combating post-operative collapse. However, the drug should not be regarded as a substitute for blood, plasma or other measures indicated in treating shock.

Like other vasopressor agents, methoxamine hydrochloride is contraindicated in patients with myocardial degeneration or coronary disease. It should be used only with great care, if at all, in patients with cardiovascular disease, hyperthyroidism or severe hypertension. In patients with hypertension, a fall in blood pressure during spinal anesthesia may be greater or more serious than in normotensive patients. Caution should be exercised to avoid overdosage resulting in high blood pressure and excessive bradycardia. High dosage occasionally may produce sustained, excessive blood pressure elevations with severe headache. Excessive dosage, especially that given intravenously, may produce headache, pilomotor response, a desire to void and projectile vomiting.

**Dosage.**—Methoxamine hydrochloride is administered in solution by either intramuscular or intravenous injection. The latter route should be reserved for emergencies or cases in which the systolic blood pressure falls to 60 mm. of mercury or less.

The usual intramuscular dose is 10 to 15 mg. When used to prevent a fall in blood pressure during spinal anesthesia, it is administered intramuscularly at the time of induction, and the dose is adjusted in accordance with the level of anesthesia to be employed; 10 mg. may be adequate for operations below the level of the umbilicus, 15 to 20 mg. for those above that level. A second dose should not be given until the previous one has had time to act; usually 15 minutes is sufficient. A solution of the drug containing 1 per cent procaine hydrochloride may be employed as the prophylactic intramuscular dose immediately prior to spinal anesthesia. From 0.1 to 0.2 cc. of such solution is used to make a skin wheal and produce local anesthesia at the site selected for lumbar puncture. After inserting the needle deeper, the remainder of the solution needed to provide the pressor dose of the drug is injected intramuscularly. Lumbar puncture is then made through the skin wheal. In combating hypotension from other causes, the intramuscular dose is similar, but for pre-operative and postoperative use for moderate hypotension, 10 mg. may be adequate.

The usual intravenous dose, reserved for emergencies only, is 5 to 10 mg. administered slowly; however, the latter amount should not be exceeded. Intravenous injection may be accompanied by supplemental, intramuscular injection of 10 to 15 mg. to provide a more prolonged effect.

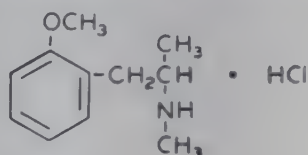
BURROUGHS WELLCOME & COMPANY, INC.

**Solution Vasoxy Hydrochloride:** 1 cc. ampuls. A solution containing 20 mg. of methoxamine hydrochloride in each cubic centimeter.

**Solution Vasoxy Hydrochloride with Procaine Hydrochloride 1%:** 1 cc. ampuls. A solution containing 15 mg. of methoxamine hydrochloride and 10 mg. of procaine hydrochloride in each cubic centimeter. Preserved with 0.1 per cent potassium metabisulfite.

U. S. patent 2,359, 707. U. S. trademark 529,974.

**METHOXYPHENAMINE HYDROCHLORIDE.**—Orthoxine Hydrochloride (UPJOHN).—2-(*o*-Methoxyphenyl) isopropylmethylamine hydrochloride.—The structural formula of methoxyphenamine hydrochloride may be represented as follows:



**Physical Properties.**—Methoxyphenamine hydrochloride is a crystalline, white powder, which is odorless and bitter. It melts between 124 and 128°. It is freely soluble in alcohol, chloroform and water and slightly soluble in ether and benzene. The pH of a 5 per cent solution is between 5.3 and 5.7.

**Actions and Uses.**—Methoxyphenamine hydrochloride is a sympathomimetic compound whose predominate actions are bronchodilatation and inhibition of the smooth muscle. Its effect on blood vessels is minimal, its pressor activity being considerably less than that of ephedrine or epinephrine.

Methoxyphenamine hydrochloride counteracts smooth muscle spasm due to pilocarpine, histamine, acetylcholine and barium chloride. It is useful as a bronchodilator in the treatment of asthma and is also effective in allergic rhinitis, acute urticaria and gastro-intestinal allergy.

The usual doses of methoxyphenamine hydrochloride produce no alterations in blood pressure and only slight cardiac stimulation. The actions on the central nervous system are minor; some patients become drowsy whereas others may be wakeful and nervous. Dryness of the mouth, nausea and faintness are less common side effects.

**Dosage.**—Adults, 50 to 100 mg., repeated every 3 or 4 hours if required. For children, a dose of 25 to 50 mg. is recommended.

#### THE UPJOHN COMPANY

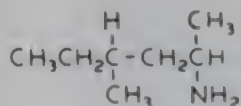
**Syrup Orthoxine Hydrochloride:** 473 cc. bottles. A flavored syrup containing 10 mg. of methoxyphenamine hydrochloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

**Tablets Orthoxine Hydrochloride:** 0.1 Gm.

U. S. trademark 509,060.



**METHYLHEXANEAMINE.**—**Forthane** (LILLY).—1,3-Dimethyamylamine.—The structural formula of methylhexaneamine may be represented as follows:



**Physical Properties.**—Methylhexaneamine is a colorless to pale yellow liquid with an ammonia-like odor. It boils between 130 and 135°. It is readily soluble in alcohol, chloroform, ether and dilute mineral acids and is very slightly soluble in water.

**Actions and Uses.**—Methylhexaneamine is a volatile sympathomimetic amine base, whose salts share the actions and uses of other vasoconstrictor agents. The systemic toxicity of methylhexaneamine in animals is greater than that of ephedrine and less than that of amphetamine. Its pressor action is more prolonged than that of epinephrine and is subject to tachyphylaxis, as shown by temporary tolerance of the peripheral arteries of animals to repeated injections. Soluble salts of the base produce mydriasis following local instillation.

Methylhexaneamine is used as an inhalant for its local vasoconstrictor action on the nasal mucosa. This treatment produces temporary relief of nasal congestion and is used as an adjunct in the treatment of allergic or infectious rhinitis and sinusitis. For this purpose the drug is supplied in the form of the carbonate which readily releases the volatile base when the inhaler is opened. This method of local application of the drug produces little or no effect upon the pulse rate or blood pressure of adult humans. If its use produces side effects such as headache, nervousness, mental stimulation or tremors, the drug should be discontinued.

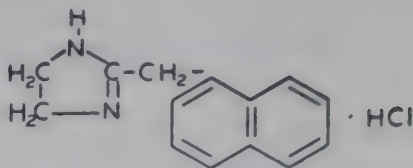
**Dosage.**—Methylhexaneamine is supplied in individual inhaler dispensers, each containing methylhexaneamine carbonate equivalent to 250 mg. of the base. One or two inhalations through each nostril is recommended as a single dose, to be repeated in accordance with the relief obtained at intervals of not less than one-half hour.

#### ELI LILLY & COMPANY

**Inhaler Forthane:** 250 mg. Each inhaler contains 250 mg. of methylhexaneamine and 32 mg. of menthol.

U. S. patents 2,350,318 and 2,386,273.

**NAPHAZOLINE HYDROCHLORIDE-U.S.P.**—**Privine Hydrochloride** (CIBA).—2-(1-Naphthylmethyl)-2-imidazoline hydrochloride.—“Naphazoline Hydrochloride, dried at 105° for 2 hours, contains not less than 98 per cent of  $\text{C}_{14}\text{H}_{14}\text{N}_2\cdot\text{HCl}$ .” U.S.P. The structural formula of naphazoline hydrochloride may be represented as follows:



**Physical Properties.**—Naphazoline hydrochloride occurs as a white, crystalline powder. It is odorless and has a bitter taste. Its solutions are neutral to litmus paper. It is freely soluble in water and alcohol, very slightly soluble in chloroform and practically insoluble in ether.

**Actions and Uses.**—Naphazoline hydrochloride is a vasoconstrictor which, when applied to nasal and ocular mucous membranes, causes a prolonged reduction of local swelling and congestion. This drug, like epinephrine, probably acts in the effector cells innervated by the sympathetic nerves.

It is of value in the symptomatic relief of disorders of the upper respiratory tract, such as nasal congestion of allergic and inflammatory origin, acute and chronic rhinitis, vasomotor rhinitis and acute and chronic rhinosinusitis. In acute nasal congestion, excessive use of vasoconstrictors may delay recovery. The rebound congestion of the mucosa sometimes caused by naphazoline hydrochloride can be alleviated within a few days simply by discontinuing all nasal medication. Those who respond with rebound congestion may tolerate solutions weaker than those commonly used. It is possible that the amount of drug absorbed following local application may be sufficient to increase the blood pressure. The drug is also useful as an ocular decongestant for symptomatic relief of bacterial, allergic and vernal conjunctivitis, to reduce blepharospasm and in the control of hyperemia of the palpebral and bulbar conjunctivae or in any condition characterized by superficial corneal vascularity.

**Dosage.**—For nasal decongestion, adults may use several drops of the 0.05 per cent or 0.1 per cent solution, depending on the relief obtained and the sensitivity of the individual mucosa. For children, the 0.05 per cent solution is suggested. Relief lasts for several hours. Occasionally, smarting and sneezing may develop.

Naphazoline hydrochloride solution is buffered to a pH of 6.2-6.3. It is affected by aluminum and should not be used in atomizers made of this material. Otherwise it may be prepared by any of the conventional methods.

For ocular decongestion an isotonic solution containing 0.1 per cent is administered by the instillation of 1 to 3 drops in the conjunctival sac of the affected eye.

#### CIBA PHARMACEUTICAL PRODUCTS, INC.

**Nasal Jelly Privine Hydrochloride 0.05%:** 20 Gm. tubes. Each gram contains naphazoline hydrochloride 0.5 mg. in a buffered water-soluble base containing glycerin, tragacanth and aromatics. Preserved with 0.01 mg. thimerosal.

**Solution Privine Hydrochloride 0.1% (Ophthalmic):** 15 cc. dropper bottles. A buffered solution containing 1 mg. of naphazoline hydro-



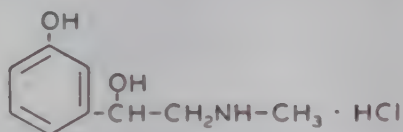
chloride in each cubic centimeter. Preserved with 0.0065 per cent methylparaben and 0.0035 per cent propylparaben.

**Solution Privine Hydrochloride 0.1% (For Adults Only):** 30 cc. bottles. A solution containing 1 mg. of naphazoline hydrochloride, 2.6 mg. of exsiccated sodium phosphate, 3.2 mg. of sodium chloride, 2.2 mg. of potassium chloride, and 7.4 mg. of potassium biphosphate in each cubic centimeter. Preserved with thimerosal 1:100,000.

**Solution Privine Hydrochloride 0.05%:** 15 cc. nebulizers and 30 cc. and 480 cc. bottles. A solution containing 0.5 mg. of naphazoline hydrochloride, 2.6 mg. of exsiccated sodium phosphate, 3.3 mg. of sodium chloride, 2.2 mg. of potassium chloride, and 7.4 mg. of potassium biphosphate in each cubic centimeter. Preserved with thimerosal 1:100,000.

U. S. patent 2,161,938. U. S. trademark 398,004.

**PHENYLEPHRINE HYDROCHLORIDE-U.S.P.—Isophrin Hydrochloride (BROEMMEL).—Neo-Synephrine Hydrochloride (WINTHROP-STEARNES).—***l*-1-(*m*-Hydroxy)- $\alpha$ -(methylaminomethyl)benzyl alcohol.—*l*-1-(*m*-Hydroxyphenyl)-2-methylaminoethanol hydrochloride.—“Phenylephrine Hydrochloride, dried at 105° for 1 hour, contains not less than 98.5 per cent of  $C_9H_{13}NO_2 \cdot HCl$ .” *U.S.P.* The structural formula of phenylephrine hydrochloride may be represented as follows:



**Physical Properties.**—Phenylephrine hydrochloride occurs as white or nearly white crystals. It is odorless and has a bitter taste. Its solutions are acid to litmus paper. It is freely soluble in water and in alcohol.

**Actions and Uses.**—Phenylephrine hydrochloride is a more powerful vasoconstrictor than synephrine tartrate; when administered orally it is a vasopressor. It is relatively nontoxic; applied to mucous membranes, it reduces swelling and congestion by contracting the small blood vessels. Phenylephrine hydrochloride may thus be useful in the symptomatic treatment of the nasal congestion accompanying such disorders of the upper respiratory tract as sinusitis, vasomotor rhinitis and hay fever. In surgery the drug is injected in combination with a soluble local anesthetic, to retard the systemic absorption of the anesthetic and to prolong its action by local vasoconstriction. It may be injected alone for vasopressor effects as a preliminary or supportive measure to combat acute hypotension in spinal anesthesia. It may be similarly employed in other acute hypotensive states due to peripheral circulatory collapse (vasomotor failure), but present evidence does not justify its use in true shock where vasomotor activity is unimpaired and the fall in blood pressure is mainly the result of the decrease in the volume



of the circulating blood. Its value as a cardiac stimulant is conjectural. A 0.2 per cent solution may be injected intravenously to combat paroxysmal tachycardia which does not respond to other methods of treatment. Phenylephrine hydrochloride may be used as a mydriatic in the eye preliminary to fundoscopic examination; in conjunction with cycloplegics in the detection of refractive errors, as an aid in the prevention or freeing of posterior synechiae and temporarily, as a vasoconstrictor to lower intraocular tension in cases of glaucoma where this effect is not counteracted by dilation of the pupil. Overdosage may induce ventricular extrasystoles and short paroxysms of ventricular tachycardia, sensation of fullness in the head and tingling of the extremities.

Preparations of phenylephrine hydrochloride are incompatible with butacaine, but other local anesthetics may and should be used beforehand to reduce the irritation produced by the 10 per cent solution or emulsion. The 0.0125 per cent, the 2.5 per cent and the 10 per cent ophthalmic solutions contain, in addition to other ingredients, 0.001 per cent of Aerosol OT 100 (dioctyl ester of sodium sulfosuccinate). Phenylephrine hydrochloride is relatively stable in alkaline solutions when protected by an antioxidant. It may be sterilized by boiling.

The pressor and anti-allergic effects of the drug are also produced by oral administration, therefore this route may be employed in the treatment of orthostatic hypotension and allergic disorders. The comparatively larger doses required for effective oral treatment are only rarely accompanied by mild gastrointestinal symptoms. These may be avoided by administering the drug after meals.

**Dosage.**—For oral administration the average dose of phenylephrine hydrochloride should be approximately fifty times the subcutaneous dose: 250 mg. given orally is approximately equivalent to 5 mg. administered subcutaneously. With this dose the pulse rate is usually decreased about 20, and the systolic pressure increased 30 mm. of mercury while the diastolic pressure is increased about 20 mm. of mercury in normal persons. After oral administration the effects are slower but more prolonged than following subcutaneous administration. In the management of orthostatic hypotension an initial dose of 150 mg. daily, decreasing to 60 mg. daily, has been successfully employed to control symptoms. In allergic states, 30 to 75 mg. daily in divided doses is recommended. In the treatment of paroxysmal tachycardia, a 0.2 per cent solution may be injected intravenously. The initial dose should not exceed 0.5 mg.; and subsequent doses, determined by the initial blood pressure response, should not exceed 0.1 to 0.2 mg.

#### BROEMMEL PHARMACEUTICALS

**Solution Isophrin Hydrochloride 0.25%:** 30 cc., 118.3 cc. and 473 cc. bottles. A buffered, isotonic solution containing 2.5 mg. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.1 per cent chlorobutanol and 0.1 per cent sodium sulfite.

**Solution Isophrin Hydrochloride Ophthalmic 0.125%:** 15 cc. and

118.3 cc. bottles. A buffered, isotonic solution containing 1.25 mg. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.01 per cent methylparaben, 0.005 per cent propylparaben, 0.01 per cent chlorobutanol and 0.1 per cent sodium sulfite.

U. S. trademark 355,953.

**WINTHROP-STEARNs, INC.**

**Capsules Neo-Synephrine Hydrochloride:** 10 mg. and 25 mg.

**Elixir Neo-Synephrine Hydrochloride:** 473 cc. and 3.78 liter bottles. A flavored alcohol solution containing 1 mg. of phenylephrine hydrochloride in each cubic centimeter.

**Emulsion Neo-Synephrine Hydrochloride 0.25% (*Intranasal*):** 30 cc. and 473 cc. bottles. A mineral oil and water emulsion containing 2.5 mg. of phenylephrine hydrochloride and 4 mg. of sodium benzoate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Emulsion Neo-Synephrine Hydrochloride 10%:** 4 cc. bottles. A mineral oil and water emulsion containing 0.1 Gm. of phenylephrine hydrochloride and 4 mg. of sodium benzoate in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite, 1 per cent ascorbic acid and 0.5 per cent chlorobutanol.

**Jelly Neo-Synephrine Hydrochloride 0.5%:** A jelly-like bland base containing 5 mg. of phenylephrine hydrochloride and 5 mg. of sodium chloride in each gram. Preserved with 0.45 per cent sodium benzoate.

**Solution Neo-Synephrine Hydrochloride 0.12%:** 15 cc. bottles. A buffered solution containing 1.25 mg. of phenylephrine hydrochloride. Preserved with 0.4 per cent chlorobutanol and 0.1 per cent sodium bisulfite.

**Solution Neo-Synephrine Hydrochloride 0.2% (*for Parenteral Use*):** 2 cc. ampuls. An isotonic solution containing 2 mg. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite.

**Nasal Solution Neo-Synephrine Hydrochloride 0.25%:** 15 cc. plastic spray bottles. A solution containing 2.5 mg. of phenylephrine hydrochloride in each cubic centimeter. Preserved with phenylmercuric acetate 1:50,000.

**Solution Neo-Synephrine Hydrochloride 0.25%:** 30 cc., 118 cc. and 473 cc. bottles. A buffered isotonic solution containing 2.5 mg. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.02 per cent methylparaben, 0.01 per cent propylparaben and 0.2 per cent sodium bisulfite.

**Solution Neo-Synephrine Hydrochloride 0.25% in Isotonic Solution of Three Chlorides (*Aromatic*):** 29.5 cc. and 473 cc. bottles. An isotonic chloride solution containing 2.5 mg. of phenylephrine



hydrochloride in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite.

**Solution Neo-Synephrine Hydrochloride 0.5% (*Intranasal*):** 30 cc. bottles. A buffered isotonic solution containing 0.5 Gm. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.02 per cent methylparaben, 0.01 per cent propylparaben and 0.2 per cent sodium bisulfite.

**Solution Neo-Synephrine Hydrochloride 1%:** 30 cc., 118 cc. and 473 cc. bottles. A buffered solution containing 10 mg. of phenylephrine hydrochloride and 5 mg. of sodium chloride in each cubic centimeter. Preserved with 0.02 per cent methylparaben, 0.01 per cent propylparaben and 0.1 per cent sodium bisulfite.

**Solution Neo-Synephrine Hydrochloride 1% (*for Parenteral Use*):** 1 cc. ampuls and 5 cc. vials. A sterile solution containing 10 mg. of phenylephrine hydrochloride and 6 mg. of sodium chloride in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite.

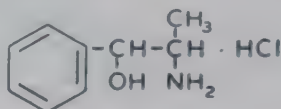
**Solution Neo-Synephrine Hydrochloride 2.5%:** 15 cc. bottles. A buffered solution containing 25 mg. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.4 per cent chlorobutanol and 0.2 per cent sodium bisulfite.

**Solution Neo-Synephrine Hydrochloride 10%:** 5 cc. bottles. A buffered solution containing 0.1 Gm. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.4 per cent chlorobutanol and 0.3 per cent sodium bisulfite.

**Ophthalmic Solution Neo-Synephrine Hydrochloride 10%:** 4 cc. tubes. A buffered solution containing 0.1 Gm. of phenylephrine hydrochloride in each cubic centimeter. Preserved with 0.4 per cent chlorobutanol and 0.3 per cent sodium bisulfite.

U. S. patent 1,932,347 and 1,954,389. U. S. trademark 406,720.

**PHENYLPROPANOLAMINE HYDROCHLORIDE.**—Propadrine Hydrochloride (SHARP & DOHME).— $\alpha$ -(1-Aminoethyl)benzyl alcohol.—The structural formula of phenylpropanolamine hydrochloride may be represented as follows:



**Physical Properties.**—Phenylpropanolamine hydrochloride is a white, crystalline powder with an odor like benzoic acid. Phenylpropanolamine hydrochloride melts between 190 and 194°. It is freely soluble in alcohol and water and insoluble in benzene, chloroform and ether. Aqueous solutions are neutral to litmus.

**Actions and Uses.**—Phenylpropanolamine hydrochloride acts similarly to ephedrine. When the aqueous solution is applied locally, it produces constriction of the capillaries, thereby shrinking the



swollen mucous membranes. It is also effective orally for the symptomatic control of allergic manifestations, such as perennial hay fever and bronchial asthma, and as an adjunct for controlling the appetite in the dietary management of obesity. Its action is more prolonged than that of ephedrine and it is not so apt to produce anxiety complex as is ephedrine. Because of its vasoconstricting action, phenylpropanolamine hydrochloride should be administered with caution to persons with heart or thyroid disease, high blood pressure or diabetes mellitus.

**Dosage.**—As a local application, spray or instillation, 1 or 3 per cent aqueous solutions; orally in allergic conditions, 25 to 50 mg. three times daily is usually adequate for adults, with correspondingly smaller doses for children; to depress appetite in obesity, 50 mg. two or three times daily before meals for adults, 10 to 15 mg. three times daily for children 5 to 7 years of age, 25 mg. three times daily for children 8 to 12 years of age.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Capsules Propadrine Hydrochloride:** 25 mg. and 50 mg.

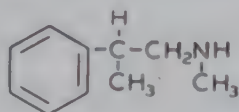
**Elixir Propadrine Hydrochloride:** 473 cc. and 3.78 liter bottles. A flavored elixir containing 4 mg. of phenylpropanolamine hydrochloride in each cubic centimeter.

**Solution Propadrine Hydrochloride 1%:** 30 cc. vials and 473 cc. bottles. An isotonic solution containing 10 mg. of phenylpropanolamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Solution Propadrine Hydrochloride 3%:** 3.78 liter bottles. An isotonic solution containing 30 mg. of phenylpropanolamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Propadrine is a U. S. registered trademark, but the firm disclaims any proprietary rights to the name.

**PHENYLPROPYLMETHYLAMINE.**—Vonedrine (MERRELL).—N,β-Dimethylphenethylamine.—The structural formula of phenylpropylmethylamine may be represented as follows:



**Physical Properties.**—Phenylpropylmethylamine is a colorless to pale yellow liquid which begins to boil at 203° and 98 per cent of which distills between 205 and 210°. It is very soluble in alcohol, benzene and ether, and 1.2 parts dissolve in 100 parts of water. Aqueous solutions of phenylpropylmethylamine are alkaline to litmus; the pH of a solution of 2 drops (about 0.1 ml.) of phenylpropylmethylamine diluted with 10 ml. of water is about 10.5.

**Actions and Uses.**—Phenylpropylmethylamine base is volatile and therefore may be inhaled to produce nasal constriction. It produces little or no irritation, local tissue reaction or central nervous system and cardiovascular stimulation.

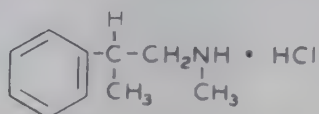
**Dosage.**—In using the phenylpropylmethylamine inhaler, one long inhalation through each nostril is usually sufficient. This may be repeated as needed, although the usual care concerning such compounds should be exercised until more information is available in the entire field of sympathomimetic amine compounds, especially those used locally as nasal vasoconstrictors.

#### THE WM. S. MERRELL COMPANY

**Inhaler Vonedrine:** Each inhaler contains (at the time of manufacture) not less than 0.25 Gm. of phenylpropylmethylamine and aromatics.

U. S. patent 2,298,630. U. S. trademark 406,970.

**PHENYLPROPYLMETHYLAMINE HYDROCHLORIDE.**—**Vonedrine Hydrochloride (MERRELL).**—N, $\beta$ -Dimethylphenethylamine hydrochloride.—Phenylpropylmethylamine hydrochloride is made by adding phenylpropylmethylamine to an aqueous solution of hydrochloric acid. It is not available in the dry state. The structural formula of phenylpropylmethylamine hydrochloride may be represented as follows:



**Physical Properties.**—The solution is clear, colorless and nearly odorless. It has a pH between 5.5 and 6.5.

**Actions and Uses.**—Phenylpropylmethylamine hydrochloride, like the volatile base, acts chiefly as a local vasoconstrictor. It is used in the form of an isotonic solution for topical application to produce shrinking of the nasal mucosa. Its local effects are accompanied with minimal irritation, local tissue reaction or secondary congestion and little or no stimulation of the cardiovascular or central nervous system. Although it is relatively nontoxic, ordinary precautions should be observed with this as with other sympathomimetic agents to avoid the possible untoward effects of over-dosage.

**Dosage.**—Phenylpropylmethylamine hydrochloride is usually applied locally in a concentration of 2.8 per cent, either as drops into the nose, as a nasal spray, as nasal tampons or by displacement followed by suction. Five to 10 drops in each nostril every 3 hours is usually sufficient to provide symptomatic relief of simple nasal congestion.

Phenylpropylmethylamine hydrochloride is incompatible with silver salts, tannates and picrates.

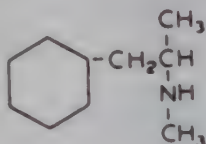
#### THE WM. S. MERRELL COMPANY

**Solution Vonedrine Hydrochloride 2.8%:** 30 cc. dropper bottles

and 473 cc. bottles. A solution containing 28 mg. of phenylpropylmethylamine hydrochloride and 0.2 mg. of cetylpyridinium chloride in each cubic centimeter. Preserved with 0.05 per cent methylparaben and 0.01 per cent propylparaben.

U. S. patent 2,298,630. U. S. trademark 406,970.

**PROPYLHEXEDRINE.**—**Benzedrex** (SMITH, KLINE & FRENCH).—N,α-Dimethylcyclohexaneethylamine. — 1-Cyclohexyl-2-methylaminopropane.—The structural formula of propylhexedrine may be represented as follows:



**Physical Properties.**—Propylhexedrine is a clear, colorless liquid with a characteristic amine odor. It boils between 202 and 206°. Propylhexedrine is very slightly soluble in water and soluble in dilute acids, alcohol and ether.

**Actions and Uses.**—Propylhexedrine is closely related to, and shares the actions and uses of, amphetamine and similar volatile sympathomimetic amine compounds. It produces vasoconstriction and a decongestant effect on the nasal mucous membranes. Propylhexedrine has only about one-half the pressor effect of amphetamine and produces decidedly less effect on the central nervous system. Propylhexedrine therefore is useful primarily for its local shrinking effect upon the nasal mucosa in the symptomatic relief of nasal congestion caused by the common cold, allergic rhinitis or sinusitis. Its volatility makes propylhexedrine convenient for intranasal application by inhalation and for reaching structures sometimes inaccessible to liquid forms of medication. Because of its wide margin of safety and relative freedom from toxic side effects, the use of propylhexedrine by inhalation is not contraindicated for patients in whom an ephedrinelike action would be undesirable. It is considered safe for self-medication by adults, but children should not have unsupervised access to an inhaler.

**Dosage.**—Propylhexedrine is administered by nasal inhalation with a portable inhaler containing 0.25 Gm. of the drug. The inhaler should be kept closed tightly between applications to avoid loss of the volatile contents. The usual dose is two inhalations through each nostril (about 0.5 mg.). This dose may be repeated as required to obtain relief. When the inhaler is cold, it should be warmed in the hand before use because the volatility of propylhexedrine is reduced by cooling. With ordinary use, a 0.25 Gm. container will retain its effectiveness 2 to 3 months.

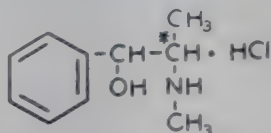
SMITH, KLINE & FRENCH LABORATORIES

**Inhaler Benzedrex:** Each inhaler contains 0.25 Gm. of propylhexedrine.

U. S. patent 2,454,746. U. S. trademarks 438,149 and 438,148.



**RACEPHEDRINE HYDROCHLORIDE-N.F.**—*Racemic*  $\alpha$ -(1-methyl-aminoethyl)benzyl alcohol hydrochloride.—*Racemic* Ephedrine Hydrochloride.—“Racephedrine Hydrochloride, when dried at 105° for 3 hours, contains not less than 80.4 per cent and not more than 82.5 per cent of anhydrous racephedrine ( $C_{10}H_{15}NO$ ), corresponding to not less than 98 per cent of  $C_{10}H_{15}NO.HCl$ .” *N.F.* The structural formula of racephedrine hydrochloride may be represented as follows:



**Physical Properties.**—Racephedrine hydrochloride occurs as fine white, odorless crystals or powder. It is affected by light. Its solutions are optically inactive. One gram of racephedrine hydrochloride dissolves in about 4 ml. of water and in about 25 ml. of alcohol. It is insoluble in ether.

**Actions and Uses.**—Racephedrine hydrochloride produces peripheral effects similar to those of epinephrine. However, it is difficult to explain fully its effects without postulating some stimulation of the central nervous system and some action on striated muscle as well as direct stimulation of sympathetically innervated smooth muscle. In small doses, racephedrine hydrochloride stimulates the heart, increasing the rate and the strength of contractions and raising the blood pressure. In large and toxic doses the drug has a depressant action on the heart muscle. On intravenous or intramuscular injection it causes a rather lasting rise of blood pressure, due mainly to vasoconstriction. Other effects similar to those of epinephrine are dilatation of the bronchi and mydriasis after local or systemic administration. On local application to mucous membranes or wounds it contracts the capillaries to a moderate degree and thus diminishes hyperemia and reduces swelling. The systemic effects can be obtained by oral administration.

Racephedrine hydrochloride is used locally to dilate the pupils of the eyes and to shrink the congested mucosa of the nostrils in rhinitis and sinusitis. It is useful in asthma, especially to prevent attacks, but it often fails partially or completely. It is also used in hay fever and urticaria. Racephedrine hydrochloride may be used to sustain the blood pressure in some types of hypotension, but it is of no benefit in shock, circulatory collapse or hemorrhage, and of limited value in preventing the muscle weakness of myasthenia gravis. It is without value in Addison's disease.

Racephedrine hydrochloride is contraindicated in hypertensive states, hyperthyroidism, insomnia, arteriosclerosis in the aged, nephritis, coronary disease and myocardial damage.

**Dosage.**—Racephedrine hydrochloride is effective whether given orally, intramuscularly, intravenously, or by any other route. For local application to mucous membranes it is used in 0.5 to 2 per cent solution; in ophthalmologic work it has been used in 4 per

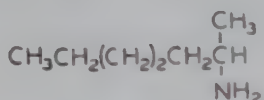
cent solution. The usual oral dose for adults is 20 mg. to 50 mg. every 3 to 4 hours.

#### THE UPJOHN COMPANY

**Capsules Racephedrine Hydrochloride:** 25 mg.

**Solution Racephedrine Hydrochloride 1%:** A Ringer's solution containing 10 mg. of racephedrine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**TUAMINOHEPTANE.**—**Tuamine (LILLY).**—1-Methylhexylamine.—The structural formula of tuaminoheptane may be represented as follows:



**Physical Properties.**—Tuaminoheptane is a colorless to pale yellow liquid which boils between 138.5 and 142.5°. It is freely soluble in alcohol, benzene, chloroform and ether and is sparingly soluble in water. The pH of a 1 per cent solution is 11.45.

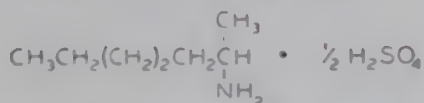
**Actions and Uses.**—This compound is a vasoconstrictor and a sympathomimetic amine. Inhalation of the vapors is an effective treatment for acute rhinologic conditions and is of added usefulness when prolonged and repeated medication is necessary (see also general statement on sympathomimetic agents). It should be used with caution by those who have cardiovascular disease.

**Dosage.**—An inhaler is available. The dosage is one or two gentle inhalations through each nostril, repeated at hourly intervals if necessary.

#### ELI LILLY & COMPANY

**Inhaler Tuamine:** Each inhaler contains (at the time of packing) the equivalent of 0.325 Gm. of tuaminoheptane and aromatics.

**TUAMINOHEPTANE SULFATE.**—**Tuamine Sulfate (LILLY).**—1-Methylhexylamine sulfate.—The structural formula of tuaminoheptane sulfate may be represented as follows:



**Physical Properties.**—Tuaminoheptane sulfate is a white, odorless powder, which is readily soluble in water. The pH of a 1 per cent solution is about 5.4.

**Actions and Uses.**—The vasoconstrictive effects of a 1 per cent solution of this compound exceed those of a similar concentration of ephedrine; 0.5 per cent solution produces about equal vasoconstrictor action. The duration of effect is greater than that of ephedrine.

**Dosage.**—A 1 per cent solution may be applied to the mucous

membranes of infants and adults by spray, dropper or tampon and is usually adequate for routine treatment. A 2 per cent solution, best applied by pledgets of cotton, may be used for operative procedures, diagnostic examination and other special circumstances. For displacement therapy, a 0.2 per cent solution can be used.

**CHEMO PURO MANUFACTURING CORPORATION**

**Powder Tuaminoheptane Sulfate:** Bulk; for manufacturing use.

**ELI LILLY & COMPANY**

**Solution Tuamine Sulfate 1%:** 30 cc. and 475 cc. bottles. A solution containing 10 mg. of tuaminoheptane sulfate, 6.8 mg. of potassium phosphate monobasic, and 0.9 mg. of sodium chloride. Preserved with phenylmercuric nitrate 1:50,000.

**Solution Tuamine Sulfate 2%:** 60 cc. and 475 cc. bottles. A solution containing 20 mg. of tuaminoheptane sulfate, and 6.8 mg. of potassium phosphate monobasic. Preserved with phenylmercuric nitrate 1:50,000.



## Blood Derivatives and Plasma Substitutes

Preserved whole blood and blood fractions are generally available to all physicians, either from blood banks, health departments or pharmaceutical houses.

Coagulation of whole blood and plasma is prevented by collecting the whole blood in cold, sterile containers containing a pyrogen-free anticoagulant, an aqueous solution composed of citric acid, citrate and dextrose (ACD). Two standard ACD solutions are approved by the National Institutes of Health for use by licensed blood banks. This method of collection is standard when the blood is to be transfused as whole blood or when the erythrocytes are to be separated from the plasma and used as packed red cells or resuspended in sterile nonpyrogenic isotonic solutions. The remaining plasma may be used as liquid plasma or processed to dried plasma or fractionated into the several plasma protein products.

When blood is to be processed without delay into liquid or dried plasma or into plasma fractions, a pyrogen-free, aqueous solution of 4 per cent trisodium citrate may be employed as the anticoagulant. A final maximum concentration of 0.3 to 0.5 per cent of the citrate salt is recommended in both instances.

Preservation of whole blood requires constant refrigeration at 4 to 6°. The addition of dextrose to a blood preservative mixture significantly retards hemolysis of the erythrocytes and permits use of the blood for transfusion purposes for a period of 3 weeks. Even under adequate refrigeration, however, changes occur rapidly in the other cellular components, especially in the neutrophilic leukocytes and platelets, and more slowly in prothrombin and complement. Therefore, whole blood preserved in ACD solution should be used as soon as possible and in no event after the expiration of 21 days. Blood collected in plain sodium citrate, on the other hand, deteriorates much more rapidly and should be used within a 5-day period. Preservation of fresh plasma requires storage either in the frozen or dried state, while liquid plasma may be stored at room temperature for use in the treatment of shock.

Untoward reactions may follow the transfusion of whole blood, serum and plasma, but they rarely follow the use of plasma fractions. Inadequate blood grouping and crossmatching, errors in technics, circulatory overload, pyrogenic substances in the transfusion equipment, allergic idiosyncrasy and bacterial contamination may be responsible for reactions to whole blood. All

but the first mentioned above may be responsible for reactions to serum or plasma. Since heat readily coagulates and modifies the blood proteins, blood, plasma, serum or serum albumin should not be warmed prior to or during transfusion.

There are generally accepted medical criteria for the selection of blood donors. In general, blood for transfusion is accepted only from healthy donors, free from any disease transmissible by transfusion, with no history of malaria or jaundice in the past and of certain other diseases within a period of a few months to years preceding donation. Usually, transmissible diseases are not a problem when blood is taken for the preparation of blood derivatives. The exception is homologous serum hepatitis (jaundice) which is carried in both blood plasma and serum, as well as in the plasma fraction containing fibrinogen. The other plasma fractions appear to be free from this potential hazard when prepared by the present standard method of fractionation. This virus is also transmitted by transfusions of whole blood and by inadequately sterilized equipment, for example, syringes, needles, tubing and glassware. While experimental evidence indicates that sufficient ultraviolet irradiation of serums and plasma will inactivate the virus of homologous serum jaundice, the usual methods now used have not proved adequate to do so in all cases. Prolonged storage at room temperature in excess of 6 months or heating at higher temperatures apparently will inactivate the virus of serum jaundice, but such treatment of plasma or serum alters the structure of the proteins to varying degrees. Whenever plasma (or serum) is stored at room temperature for up to 2 years, it remains useful for the treatment of shock.

Whole blood is used for transfusion when it is desirable to administer the cellular blood elements and to supplement the diminished blood proteins. Either packed red cells or concentrated, compatible, blood cell suspensions in pyrogen-free, isotonic solutions can be used to replenish blood cell volume diminished by hemorrhage or blood dyscrasias when loss of red cells is the significant problem. However, it is important that transfusions of whole blood or of red cells be given only when truly indicated, since there is always some hazard of transmitting homologous serum jaundice.

The cell-free liquid portion of uncoagulated blood is plasma, while the fluid portion which remains when the cellular elements have been removed by coagulation is called serum. Blood plasma contains the three major blood proteins—albumin, globulin and fibrinogen; blood serum contains albumin and globulin only, the fibrinogen having been removed during the process of coagulation. Blood serum and plasma contain not only the proteins but also carbohydrates, fats, inorganic and organic salts, hormones, enzymes, vitamins and other soluble elements. Serum and plasma are used to restore diminished circulating blood volume in the treatment of shock and to supplement essential blood proteins lost through hemorrhage, burns, malnutrition and certain hemorrhagic blood dyscrasias. Both serum and plasma can be reduced by drying from the free state (free drying) to sterile dry powders



which are easily reconstituted by the addition of sterile, pyrogen-free water. For plasma, a 0.1 per cent solution of citric acid is used to avoid loss of the labile components, such as prothrombin and complement.

The blood plasma proteins—albumin, globulin and fibrinogen—can be separated by electrophoresis, ultracentrifugation and fractional precipitation by salts or organic solvents to yield highly purified products. In the fractionation of blood plasma, the standard method in wide use today is the cold-ethanol method developed during World War II. The protein fractions are not necessarily homogeneous as several different globulins (alpha, beta and gamma) have been isolated. Gamma globulin contains the greatest concentration of the antibodies used therapeutically or prophylactically for passive immunization against infectious diseases.

Therapeutic immune serums and serum derivatives currently licensed by the National Institutes of Health are: chicken pox immune serum, measles immune serum, mumps immune serum, pertussis immune serum, poliomyelitis immune serum, scarlet fever immune serum, poliomyelitis immune globulin and immune serum globulin (effective for measles and infectious hepatitis prophylaxis). The only difference between the two gamma globulin preparations last mentioned is that the poliomyelitis immune globulin has been tested for and found to contain a stipulated amount of antibody to the Lansing strain of the poliomyelitis virus. The differences between the immune serums and the immune globulin preparations are: (1) the antibodies are much more concentrated in the globulin preparations, which are a 16 per cent solution of the protein, and (2) the globulin preparations can be administered only intramuscularly or subcutaneously, while the serums can be given intravenously as well. (See the chapter on immunologic agents for complete discussion.)

In addition to the gamma globulin fraction, the other useful protein fractions of plasma are fibrinogen (also processed into fibrin film and fibrin foam) and normal serum albumin. These products are also licensed by the National Institutes of Health. Fibrinogen contains antihemophilic globulin and is useful in the control of bleeding in hemophiliacs. Some evidence being accumulated indicates that this fraction also is useful in other types of uncontrolled bleeding due to unknown causes. Fibrin foam is prepared by mixing the fibrinogen with thrombin and beating it with air. The foam is used surgically to aid in the control of bleeding. Fibrinogen and thrombin also have been used as a means of forming a coagulum around renal calculi so that they may be easily and completely removed surgically. Fibrin films, prepared by mixing fibrinogen with thrombin so that a stable film is formed, are used particularly as a substitute for the dura mater in operations on the brain, as well as for some other procedures where this type of a preparation aids in surgical repair.

Blood grouping and typing reagents (serums), prepared from human blood, are essential for determining blood groups and types. The international classification (Landsteiner) of blood groups as



O (universal donor), A, B and AB (universal recipient) is widely accepted and is used by blood banks all over the country. Specific serums for determining the subgroups of A are also available, as are specific serums for some of the minor blood groups. The determination of the Rh type of the donor and of the recipient as either positive or negative has become routine in blood transfusion procedures, while the determination of specific Rh subtypes usually is carried out only when a question of isosensitization to one of the Rh factors is being investigated. Group specific A and B substances are used primarily to reduce the titer of anti-A and anti-B agglutinins in group O blood when it is to be used as universal donor blood in emergencies. Such products licensed by the National Institutes of Health for commercial production are:

1. Diagnostic Serums

- Anti-A Blood Grouping Serum
- Anti-B Blood Grouping Serum
- Anti-A and B Blood Grouping Serum (Group O)
- Absorbed Anti-A Blood Grouping Serum (Sub-Group A<sup>1</sup>)
- Group AB Serum

2. Anti-Rh Typing Serums

- Anti-Rh<sub>0</sub> (Anti-D)
- Anti-Rh<sub>0</sub>' (Anti-CD)
- Anti-Rh<sub>0</sub>" (Anti-DE)
- Anti-Rh<sub>0</sub> rh' rh" (Anti-CDE)
- Anti-rh' (Anti-C)
- Anti-rh" (Anti-E)
- Anti-hr' (Anti-c)
- Anti-hr" (Anti-e)

3. Others

- Anti-K Serum (Anti-Kell)
- Anti-Fy<sup>a</sup> Serum (Anti-Duffy)
- Anti-M Serum
- Anti-N Serum
- Blood Group Specific Substance A
- Blood Group Specific Substance B
- Blood Group Specific Substances A and B

For many years, dating back as far as World War I, there has been a continuous search for an acceptable and adequate "blood substitute." There is no substitute for whole blood, but research has developed some acceptable and satisfactory "plasma substitutes," also called plasma volume expanders. Many substances have been investigated for this purpose, including acacia, pectin and a number of synthetic chemical compounds. Most of these have proved to be either clinically inadequate or medically unsafe. This area of research has included investigation into the possibilities of purifying animal proteins as a substitute for human plasma. It has thus far not proved possible to despeciate such proteins sufficiently to avoid a question of sensitivity reactions of the anaphylactic type.

Two plasma substitutes currently are approved by the National

Research Council and accepted by the Food and Drug Administration. These are gelatin and dextran. A refined 6 per cent solution of gelatin (from beef bone collagen) provides a safe and clinically effective plasma substitute. However, this solution is a gel at room temperature and requires warming both before and during transfusion. This characteristic makes gelatin solution unsatisfactory for emergency field use. Dextran is the other approved plasma substitute and also is used as a 6 per cent solution. It is prepared by hydrolyzing sucrose with the bacterial organism *Leuconostoc mesenteroides* to produce a water-soluble, high molecular weight, glucose polymer. Some difficulty with mild to moderately severe allergic reactions has been encountered during the experimental work with this product, but this problem has been almost completely eliminated by refinements in the processing technics. It remains fluid to below freezing temperatures and, therefore, is the most satisfactory emergency plasma substitute available commercially. It is important to remember that both of these products, gelatin and dextran, as well as any of the other substances currently under investigation, are only temporarily effective in the severely injured patient, and whole blood (for burns, plasma or serum albumin also may be used) must be administered within 12 to 18 hours.

Other plasma substitutes under current investigation include polyvinylpyrrolidone (PVP), a high polymer product of the reaction, under high pressure, of formaldehyde, acetylene and a catalyst. It was used extensively and successfully by the Germans during World War II and gives excellent clinical results; however, it is stored in body tissues, including the reticulo-endothelial system, for relatively long periods of time with a slow excretion rate. Experimental investigation is still under way to determine whether or not such storage can possibly cause significant pathologic changes in the human body. Other substances under investigation include modified human globin, oxypolygelatin and polymerization products of some of the dextrans.

## BLOOD DERIVATIVES

**NORMAL HUMAN SERUM ALBUMIN-U.S.P.**—"Normal Human Serum Albumin is a sterile solution of the serum albumin component of blood from healthy donors. It is prepared by a fractionation process. Normal Human Serum Albumin complies with the official requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Physical Properties.**—Normal human serum albumin is a moderately viscous, clear, brownish liquid. It is substantially odorless.

**Actions and Uses.**—Normal human serum albumin is used to reduce edema and raise the serum protein level in hypoproteinemia; it is also used in the treatment of shock.

**Dosage.**—Approximately 2.2 cc. per kilogram of body weight is given at a rate not greater than 2 cc. per minute, usually accompanied by physiologic salt solution or 5 per cent glucose.



## CUTTER LABORATORIES

**Normal Human Serum Albumin (Salt-Poor) 25%:** 20 cc. bottles, containing 5 Gm. of albumin with not more than 0.33 per cent of sodium in a buffered diluent, osmotically equivalent to 100 cc. of plasma. No preservative added.

Licensed by Research Corporation. U. S. patent No. 2,390,074.

**ANTIHEMOPHILIC PLASMA (HUMAN).**—Irradiated antihemophilic plasma (human) is the sterile plasma prepared in a manner to prevent destruction of the relatively labile active fraction by pooling plasma obtained by centrifuging whole blood from approximately 20 donors. After sterilization by ultraviolet irradiation, the product is dried from a frozen state under high vacuum. The product meets the requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—Antihemophilic plasma (human) is human plasma processed so as to prevent denaturation of the antihemophilic globulin component present in freshly prepared plasma. It is administered for the temporary reduction of the dysfunction of the hemostatic mechanism in hemophilia.

**Dosage.**—Antihemophilic plasma (human) is administered intravenously. It is employed as a solution, prepared by restoration of a freeze-dried preparation equivalent to either 60 or 120 cc. of citrated liquid plasma with either 25 to 50 or 50 to 100 cc. of water for injection, depending on the volume to be used. Each 60 cc. equivalent of citrated liquid plasma, which is equivalent to 50 cc. of original plasma or 100 cc. of circulating whole blood, will maintain a normal clotting time for several hours to 2 days. This dose is usually sufficient for children; twice this amount may be required for adults. The maintenance dosage is dependent upon the weight and response of the patient. Injections should be repeated so as to maintain normal clotting time; repeated doses do not lose their effectiveness.

## HYLAND LABORATORIES

**Dried Antihemophilic Plasma (Human):** 50 and 100 cc. bottles of plasma plus anticoagulant dried from the frozen state, packaged with 50 and 100 cc. of 0.1 per cent citric acid diluent, respectively.

**IMMUNE SERUM GLOBULIN (HUMAN)-U.S.P.**—See the chapter on immunologic agents.

**NORMAL HUMAN PLASMA-U.S.P.**—Citrated Normal Human Plasma.—“Normal Human Plasma is the sterile plasma obtained by pooling approximately equal amounts of the liquid portion of citrated whole blood from eight or more adult humans. It has been treated with ultraviolet irradiation for the purpose of destroying possible bacterial and viral contaminants. Only those persons may serve as a source of Normal Human Plasma who are in physical condition to give blood and are free of those diseases transmissible by transfusion of ultraviolet irradiated plasma, as far as can be determined from the donor's personal history and from such physi-



cal examination and clinical tests as appear necessary for each donor on the day upon which the blood is drawn.

"Each bleeding is drawn under aseptic precautions into individual sterile centrifuge bottles already containing 50 cc. of a sterile 4 per cent solution of sodium citrate in water for injection for each 500 cc. of whole blood. The cell-free plasma is separated by centrifugation in the individual bottles, and transferred to a pool by means of a closed system. Sterility tests are made and the plasma is distributed into final containers through a closed system. Normal Human Plasma complies with the requirements of the National Institutes of Health of the United States Public Health Service.

"Normal Human Plasma may be dispensed as liquid, frozen, or dried plasma.

"Plasma for processing to liquid or frozen forms may also be recovered from citrated whole blood intended for whole blood transfusion when *Anticoagulant Acid Citrate Dextrose Solution* is used in the amount of 75 cc. of Solution A or 125 cc. of Solution B for each 500 cc. of whole blood."

**Physical Properties.**—Normal human plasma may be dispensed as liquid plasma, as frozen plasma or as dried plasma. Normal human plasma must be free from harmful substances, detectable by animal inoculation or by other means, and must not contain an excessive amount of preservative.

**Actions and Uses.**—Citrated normal human plasma is administered in the treatment of surgical and traumatic shock, in the treatment of burns when available plasma is lost, to combat hypoproteinemia and as a temporary substitute when whole blood is not immediately available for the treatment of hemorrhage. Plasma and serum may be considered satisfactory substitutes for whole blood *except in those cases in which the administration of red blood corpuscles is essential.*

**Dosage.**—Citrated normal human plasma, whole or restored, is administered intravenously in amounts equivalent to those employed in the transfusion of whole blood, but plasma represents approximately one-half the total volume of whole blood. "Usual dose—Intravenous 500 cc." *U.S.P.*

#### COURTLAND LABORATORIES

**Normal Human Plasma (Dried):** 50, 250 and 500 cc. bottles of dried plasma, packaged with an air filter, double pointed needle and 50, 250 and 500 cc., respectively, of 0.1 per cent citric acid solution for restoration.

#### CUTTER LABORATORIES

**Normal Human Plasma (Dried):** Equivalent to 250 cc. restored plasma, packaged with 250 cc. of 0.1 per cent citric acid in distilled water as diluent.

#### HYLAND LABORATORIES

**Normal Human Plasma (Citrated):** Equivalent to 250 cc. pooled plasma containing 5 per cent dextrose.

**Normal Human Plasma (*Dried*):** Equivalent to 50 cc., 250 cc. and 500 cc., respectively, of restored plasma packaged with 50 cc., 250 cc. and 500 cc. of 0.1 per cent citric acid in distilled water as diluent.

**JUNIOR LEAGUE BLOOD CENTER OF MILWAUKEE, INC.**

**Normal Human Plasma (*Citrated*):** Equivalent to 250 cc. of pooled plasma containing 5 per cent dextrose.

**MICHAEL REESE RESEARCH FOUNDATION**

**Normal Human Plasma (*Citrated*):** Equivalent to 50 cc., 250 cc. and 500 cc. pooled plasma containing 5 per cent dextrose. The 250 cc. unit is provided either with or without an added 250 cc. of isotonic solution of sodium chloride.

**Normal Human Plasma (*Dried*):** Equivalent to 250 cc. of pooled original plasma packaged with a double pointed needle and 300 cc. of 0.1 per cent citric acid solution for restoration.

**SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.**

**Lyovac Normal Human Plasma (*Dried*):** 50 cc., 250 cc. and 500 cc. bottles of dried plasma, packaged with a double pointed needle and 50 cc., 250 cc. and 500 cc., respectively, of 0.1 per cent citric acid solution for restoration.

U. S. patent 2,176,004. U. S. trademarks 357,061 and 380,366 (Lyovac).

**NORMAL HUMAN SERUM-N.F.**—"Normal Human Serum is the sterile serum obtained by pooling approximately equal amounts of the liquid portion of coagulated whole blood from eight or more humans who have been certified by a qualified doctor of medicine as free from any disease which is transmissible by blood transfusion at the time of drawing the blood. Each bleeding is drawn under aseptic precautions into individual sterile centrifuge bottles and allowed to coagulate for at least 12 hours but not more than 24 hours. The cell-free serum is separated by centrifugation, and transferred to a pool by means of a closed system. Sterility tests are made, a preservative is added, the serum is passed through a bacteria-excluding filter and distributed into the final containers through a closed system. *Caution:* Each lot of serum shall be aged in the liquid state for at least 28 days at 2 to 10 C. subsequent to the removal of the clot and prior to its use as liquid serum, or prior to freezing and drying. Normal Human Serum must be free from harmful substances detectable by animal inoculation and must not contain an excessive amount of preservative.

"Normal Human Serum complies with the requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Actions, Uses and Dosage.**—See the monograph on normal human plasma.

**MICHAEL REESE RESEARCH FOUNDATION**

**Normal Human Serum:** 20 and 250 cc. bottles.



## PLASMA SUBSTITUTES

**DEXTRAN.** — **Expandex** (COMMERCIAL SOLVENTS). — **Gentran** (BAXTER). — **Plavolex** (WYETH). — Dextran is a water-soluble, high molecular weight glucose polymer produced by the action of *Leuconostoc mesenteroides* on sucrose. The marketed product has an average molecular weight of about 75,000.

**Actions and Uses.**—Dextran, when partially hydrolyzed to suitable viscosity and fractionated to provide an average molecular size of 75,000, is useful for intravenous administration in a 6 per cent solution of isotonic sodium chloride to expand plasma volume and maintain blood pressure in emergency treatment of hemorrhagic and traumatic shock. It should neither be regarded as a "substitute" for whole blood or its derivatives essential in restoring blood proteins nor for combating anemia secondary to hemorrhage or severe traumatic injury such as extensive burns and fractures. Although approximately osmotically equivalent to serum albumin, 6 per cent dextran injection in saline solution is not suitable for use in the treatment of edema secondary to hypoproteinemia. Decrease in total serum proteins and hematocrit values, persisting for 6 to 24 hours, is a characteristic response to dextran injection. This is attributed partly to hemodilution, although hematocrit values occasionally return to normal before the total serum proteins. The effect on blood volume of a single injection of 500 to 1000 cc. of a 6 per cent solution usually persists for 24 hours.

Dextran is excreted in the urine to the extent of 30 to 50 per cent, and studies in progress indicate that the remainder is metabolized in the body. Specific gravity of the urine is increased as a result of renal excretion, but this returns to normal after dextran has been eliminated. When given to patients not in shock, 500 cc. of the 6 per cent solution produces no alteration in body temperature, pulse rate, respiration or blood pressure, during or after the period of injection. Vital capacity also is unchanged. As a result of expanding plasma volume, venous pressure is increased from 10 to 30 mm. of water and cardiac output is elevated concurrently. Renal and hepatic functions are not altered by dextran.

Virtually no adverse reactions have been observed following repeated injections of dextran; however, this polysaccharide has the apparently inherent tendency to produce reactions of an antigen-antibody type in certain human subjects. Such reactions are of low incidence and mild character in adequately hydrolyzed and refined preparations, which provide an average molecular size approximating that of serum albumin. As solutions of dextran do not require refrigeration, they are stored easily and are ready for immediate use in emergencies.

**Dosage.**—Dextran is administered intravenously as a 6 per cent solution in isotonic sodium chloride. The usual dose is 500 cc. infused at the rate of 20 to 40 cc. per minute, so that the total amount is administered over a period of about 15 to 30 minutes. Repeated injections may be given when necessary if blood or its derivatives are not available or subsequently indicated. For hemor-



rhage, the dosage should be limited to an amount sufficient to elevate the systolic blood pressure to not more than 80 to 85 mm. of mercury to avoid the production of further bleeding and dangerous dilution of the circulating blood. For shock associated with hemorrhage, severe burns and traumatic injuries, blood has preference over plasma or artificial colloids.

#### ABBOTT LABORATORIES

**Solution Dextran 6%:** 250 and 500 cc. bottles. An isotonic solution containing 60 mg. of dextran in each cubic centimeter. The 500 cc. containers are available with or without Venoset (disposable venoclysis unit).

#### BAXTER LABORATORIES, INC.

**Solution Gentran 6%:** 250 and 500 cc. bottles. An isotonic solution containing 60 mg. of dextran in each cubic centimeter. The 500 cc. containers are available with or without sterile administration set.

#### COMMERCIAL SOLVENTS CORPORATION

**Solution Expandex 6%:** 250 and 500 cc. bottles. An isotonic solution containing 60 mg. of dextran in each cubic centimeter. The 500 cc. containers are available with or without a disposable syringe.

#### HYLAND LABORATORIES

**Solution Dextran 6%:** 250 and 500 cc. bottles. An isotonic solution containing 60 mg. of dextran in each cubic centimeter. The 500 cc. containers are available with or without sterile administration set.

#### WYETH LABORATORIES, INC.

**Solution Plavolex 6%:** 500 cc. bottles. An isotonic solution containing 60 mg. of dextran in each cubic centimeter.

**GELATINE SOLUTION, SPECIAL INTRAVENOUS.**—A 6 per cent sterile, pyrogen-free, nonantigenic solution of gelatine in isotonic sodium chloride for use as an infusion colloid. The gelatine is specially prepared from refined beef bone collagen.

**Physical Properties.**—The gelatine solution is odorless, clear, amber colored and slightly viscous at temperatures above 29°, but gels at ordinary room temperature. It has a saline taste due to the added sodium chloride (0.9 per cent). The pH of the solution is between 6.95 and 7.40.

**Actions and Uses.**—Special intravenous gelatine solution is specially prepared for injection as a readily available infusion colloid to support blood volume in various types of shock. It is thus used as an osmotically effective substitute for plasma and whole blood when these substances are not otherwise indicated or are not available to meet emergency demands for restoring circulatory volume. In acute or recurrent hemorrhage or shock associated with loss of blood, whole blood is preferable to any substitute.

Special intravenous gelatine solution is largely excreted by the kidney and therefore should not be employed when there is renal impairment; it must be used with care in the presence of cardiac impairment to avoid the undue burden to the circulation of excessive fluid volume. Until further information is available it should not be used in the crush syndrome or in extensive third degree burns because these are associated with possible renal damage.

Since infused gelatine produces pseudoagglutination of the red blood cells that may interfere with typing or cross matching when blood transfusion is to be given later, these tests should be performed before gelatine is used.

**Dosage.**—Special intravenous gelatine solution should be warmed to about 50° before injection because the solution gels at lower room and refrigerator temperatures. It is completely fluid at body temperatures and must be kept warm for prolonged administration by the drip method. It can be given safely at rates up to 30 cc. per minute. Usually, 500 cc. is adequate for a single infusion. About 50 per cent of the gelatine remains in the circulation after 24 hours, so that a single infusion usually gives osmotic protection for 24 to 48 hours.

CHARLES B. KNOX GELATINE COMPANY, INC.

**Special Intravenous Gelatine Solution 6%:** 500 cc. bottles. A solution containing 60 mg. of gelatine in each cubic centimeter.

## AGENTS FOR BLOOD GROUPING

**BLOOD GROUP SPECIFIC SUBSTANCES A AND B.**—A sterile solution of polysaccharide-amino-acid complexes, capable of reducing the titer of the anti-A and anti-B isoagglutinins of group O donor blood. Blood group specific substance A is isolated as a precipitate from a tryptic digest of hog gastric mucin. Group specific substance B is isolated as a precipitate from a tryptic digest of the glandular portion of horse gastric mucosa.

**Actions and Uses.**—Blood group specific substances A and B, when added to group O blood, renders the latter reasonably safe for transfusions into patients having blood of another group. While this minimizes reaction attributable to the corresponding isoagglutinins, it should be kept in mind that group O blood may continue to give rise to reactions due to pyrogens, Rh incompatibility and immunologic unknowns.

**Dosage.**—Blood group specific substances A and B may be added to group O blood just prior to administration or at the time of collection and storage. One transfusion unit (10 cc.) is capable of reducing the anti-A and anti-B isoagglutinin titer of 500 cc. of group O blood to at least one-fourth of its original titer.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Solution Blood Group Specific Substances A and B:** 10 cc. vials Preserved with 0.3 per cent phenol.

U. S. patent reissue No. 22,208.



## Agents Affecting Blood Formation and Coagulation

Life is dependent upon a delicate balance within the blood itself and also within the walls of its container—namely the entire vascular system. Hemorrhage and thrombosis occur almost constantly in man and in other organisms, for the most part in minute areas. An imbalance in one direction resulting in a major thrombosis or in a hemorrhage may be disabling or fatal. The substances discussed in this chapter are designed to aid in the correction of such imbalance when it occurs either locally or general throughout the system.

The substances having a purely local effect are for the most part directed toward acceleration of coagulation, such as the combat of hemorrhage, when applied directly to bleeding surfaces. These include thrombin, gelatin foam, fibrin foam, oxidized gauze and thromboplastic brain extracts. They are useful to combat oozing from minute vessels but should not be expected to control bleeding from arteries or veins when there is appreciable pressure at the bleeding point from within the bleeding vessel.

The substances having a general effect on this balance include several anticoagulants which decrease the tendency toward thrombosis. Of these, heparin was the first to be successfully used in man. It produces a prolongation of the clotting time as measured by the Lee-White method with a lesser effect on the prothrombin time. Heparin is used most commonly at present when a rapid effect is desired to prevent or control thrombo-embolic conditions. Its major disadvantage is its ineffectiveness when administered orally. The action of heparin is limited to a few hours, unless it is administered in a vehicle from which absorption and utilization are retarded.

Numerous compounds are now being developed which are effective orally and which affect primarily the prothrombin activity and in some instances other clotting factors, such as factors V and VII. These include bishydroxycoumarin, cyclocoumarol, ethyl biscoumacetate and phenindione. Their disadvantages include much greater lag between administration and action than after the use of heparin and the need for tests for prothrombin activity in order to control the dosage. These substances are all effective against thrombo-embolism but not universally so; all may be responsible for hemorrhage in the event of overdosage or in the presence of pathologic conditions conducive to easy bleeding.

To combat excessive hypoprothrombinemia, water-soluble an-

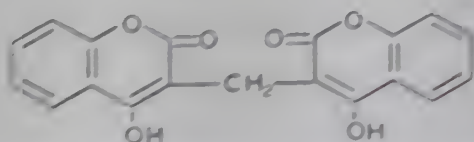


l-soluble vitamin K preparations are used effectively. The latter are more potent but also more difficult and costly to prepare. Such preparations are discussed in the chapter on vitamins. This present chapter includes agents which influence the production of normal red corpuscles in the bone marrow and the quantity of iron held within them. These include dried stomach preparations which have been demonstrated to produce definite reticulocyte and red cell response. In general, these follow the type of response which has been obtained by active liver preparations given orally or parenterally. Stomach and liver preparations may be combined effectively. More recently, folic acid and cyanocobalamin have been found to be effective in the stimulation of red cell formation. A discussion of their actions will be found in the chapter on vitamins.

Ferrous sulfate is an effective agent for the treatment of iron deficiency anemias. It may produce diarrhea in some patients.

## ANTICOAGULANTS

**BISHYDROXYCOUMARIN-U.S.P.**—Dicumarol.—3,3'-Methylenebis(4-hydroxycoumarin).—"Bishydroxycoumarin, dried at 105° for 2 hours, contains not less than 98 per cent of  $C_{12}H_8O_6$ ." *U.S.P.* The structural formula of bishydroxycoumarin may be represented as follows:



**Physical Properties.**—Bishydroxycoumarin is a white or creamy-white, crystalline powder. It has a faint, pleasant odor and a slightly bitter taste.

**Actions and Uses.**—Bishydroxycoumarin prolongs the prothrombin time by decreasing the prothrombin concentration of the blood. Although the exact mode of action is not known, it is assumed that bishydroxycoumarin acts on the liver to retard prothrombin production, since the circulating prothrombin present in blood is not affected in vitro by the addition of bishydroxycoumarin; the development of the bishydroxycoumarin effect requires 12 to 72 hours and persists for 24 to 96 or more hours after discontinuance of therapy.

Bishydroxycoumarin may be used in the prophylaxis and treatment of intravascular clots, postoperative thrombophlebitis, pulmonary embolism, acute embolic and thrombotic occlusion of peripheral arteries and recurrent idiopathic thrombophlebitis.

Bishydroxycoumarin does not directly affect thrombi or emboli already present nor does it increase the local blood supply of an area affected by an embolus. Bishydroxycoumarin retards further intravascular clotting and prevents propagation of the thrombus or embolus. In addition it permits dissolution of thrombi, presumably by the enzyme systems of the blood.

Since the ultimate outcome of acute coronary thrombosis depends largely upon extension of the clot and upon the formation of mural thrombi in the heart chambers with subsequent embolization, bishydroxycoumarin is used as an adjunct in the treatment of this condition.

As with all coumarin derivatives, large doses of salicylates may enhance the action.

**Dosage.**—Prothrombin clotting time should be determined every day during early stages of therapy. For long-term therapy, prothrombin clotting time tests should be performed once in 3 to 7 days. Until the time is 30 seconds, 200 to 300 mg. of bishydroxycoumarin is given each day. If it reaches between 30 and 35 seconds, dosage should be reduced to 50 to 100 mg. daily, and if it rises to 35 seconds or more, the drug should be withheld and not re-employed until the prothrombin time returns to 30 seconds or less. Bishydroxycoumarin may then be given cautiously in 100 mg. doses. If hemorrhagic manifestations ensue, 50 to 100 mg. of menadione sodium bisulfite may be given by slow intravenous injection (250 to 500 mg. of vitamin K<sub>1</sub>, orally). This treatment for hemorrhage may be supplemented by transfusions of fresh whole blood.

#### ABBOTT LABORATORIES

Tablets Dicumarol: 25 mg., 50 mg. and 0.1 Gm.

#### ELI LILLY & COMPANY

Pulvules Dicumarol: 25 mg., 50 mg. and 0.1 Gm.

#### SCHIEFFELIN & COMPANY

Tablets Dicumarol: 0.1 Gm.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION.

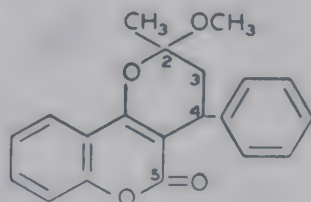
Capsules Dicumarol: 50 mg. and 0.1 Gm.

#### THE UPJOHN COMPANY

Tablets Dicumarol: 0.1 Gm.

U. S. trademark 398,198. Dicumarol is the registered collective trademark of the Wisconsin Alumni Research Foundation which controls the use thereof.

**CYCLOCUMAROL.**—Cumopyran (ABBOTT).—3,4-Dihydro-2-methoxy-2-methyl-4-phenyl-2H,5H-pyrano[3,2-c] [1]-benzopyran-5-one.—The structural formula for cyclocumarol may be represented as follows:



**Physical Properties.**—Cyclocumarol is a white, crystalline powder

with a slight odor. It melts between 164° and 168°. It is insoluble in water and slightly soluble in alcohol.

**Actions and Uses.**—Cyclocumarol, a synthetic anticoagulant related chemically and therapeutically to bishydroxycoumarin, produces its effect by lowering the blood concentration of prothrombin. It is useful, therefore, in the prophylaxis and treatment of intravascular clotting for the same purposes which have been recognized for other similar anticoagulants. See the monograph on bishydroxycoumarin.

Cyclocumarol is approximately two to three times as potent as bishydroxycoumarin and its onset of effect is sometimes more rapid and often somewhat more prolonged. However, studies so far completed do not substantiate the view that cyclocumarol may be less toxic to small blood vessels and capillaries than therapeutically equivalent amounts of other anticoagulants or that its use minimizes frequent variations in the prothrombin level, which may occur with shorter-acting anticoagulants.

Cyclocumarol is effective orally and should be administered with the same precautions observed for similar anticoagulants to avoid overdosage and hemorrhage. Little or no gastro-intestinal disturbance has been encountered with its use. Facilities should be available for making daily prothrombin determinations for the first stages of treatment and every 3 to 7 days for long-term therapy. For overdosage, blood transfusion and oral or parenteral administration of vitamin K should be used. Patients should be regularly observed for evidence of bleeding.

**Dosage.**—Initially, 0.1 to 0.2 Gm. is administered orally depending on the size and condition of the patient and the prior blood prothrombin level. Somewhat smaller doses are usually sufficient for patients with cardiac decompensation or myocardial infarction. The onset of effect usually occurs within 24 hours and the full therapeutic effect on prothrombin clotting time is usually reached within 36 hours. When the situation requires more prompt anticoagulant effect, heparin sodium may be administered to institute therapy. After the initial dose, prothrombin time is determined daily for the first 10 days to estimate the daily dosage to be administered at one time. If the prothrombin time is less than 35 seconds (control, 14 to 16 seconds), 12.5 to 50 mg. is administered daily. It is necessary to eliminate the drug on days when the prothrombin time exceeds 35 seconds.

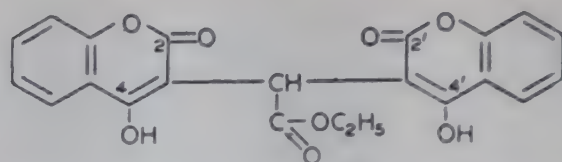
#### ABBOTT LABORATORIES

**Tablets Cumopyran: 25 mg. and 50 mg.**

Manufactured by license from Wisconsin Alumni Research Foundation under U. S. patent 2,427,579. U. S. trademark 566,359.

**ETHYL BISCOUMACETATE.**—Tromexan Ethyl Acetate (GEIGY).—3,3'-Carboxymethylene bis-(4-hydroxycoumarin) ethyl ester.—The structural formula for ethyl biscoumacetate may be represented as follows:





**Physical Properties.**—Ethyl biscoumacetate is a white, odorless, bitter, crystalline solid which melts between 177 and 182°. Another form of the solid exists which melts between 154 and 157°. It is soluble in acetone and benzene, slightly soluble in alcohol and ether and insoluble in water.

**Actions and Uses.**—Ethyl biscoumacetate is a synthetic derivative of bishydroxycoumarin and similarly produces anticoagulant action by prolonging the prothrombin time through reduction of the prothrombin concentration of the blood. See the monograph on bishydroxycoumarin.

Ethyl biscoumacetate is effective orally, alone or as an adjunct to heparin sodium, for the prevention and treatment of conditions characterized or complicated by intravascular clotting. Compared with bishydroxycoumarin, ethyl biscoumacetate possesses the properties of more rapid absorption, action, detoxification and excretion, as well as shorter action and reduced cumulative effect. Reduced cumulative effect does not imply complete freedom from the danger of cumulative action inherent in the use of internal anticoagulants. Physicians must guard carefully against overdosage to avoid the development of hemorrhagic complications. The drug is contraindicated in the presence of hemorrhagic diathesis and should be used with caution in patients with impaired hepatic or renal function.

**Dosage.**—1.5 Gm. orally at once or in divided doses is recommended as the average adult dose for the initial 24-hour period of treatment; subsequently adults usually require between 0.6 and 0.9 Gm. per day. With these amounts a therapeutic degree of hypoprothrombinemia is usually achieved within 18 to 30 hours. A more even prothrombin level may be maintained by administering the total daily amount in divided doses, such as 0.3 Gm. two or three times a day. In patients with impaired hepatic or renal function, or in whom an exaggerated response is anticipated, a smaller than average initial dose is advisable. Following the initial dosage, maintenance doses should be regulated by the results of blood prothrombin determinations. When anticoagulant therapy is used in the hospital or for ambulatory patients, close supervision with frequent determinations of the prothrombin time is essential. For most purposes it is customary to prolong the prothrombin time to two or two and one-half times the normal. Daily determinations should be made during the first several days of treatment to determine the safe and effective dosage for each patient. Thereafter, determinations on alternate days or once or twice weekly may be sufficient. Prothrombin times of 25 to 35 seconds are considered of optimal therapeutic value. When 35 seconds is exceeded, the dosage should be reduced. When the situation requires more prompt anticoagulant effect than can be obtained by the use of

ethyl biscoumacetate alone, heparin sodium may be used to institute therapy.

The action of the drug may be enhanced by the administration of salicylates which depress the prothrombin level. Hemorrhage or other evidence of serious overdosage should be treated by prompt withdrawal of the drug, intravenous or oral administration of menadione sodium bisulfite or vitamin K, and, if gross hemorrhagic manifestations ensue, repeated transfusions of fresh, whole, citrated blood or plasma until the prothrombin level returns to a safe concentration. Elevation of prothrombin time to 75 seconds not associated with hemorrhage usually returns to a near normal range within 12 to 24 hours after prompt withdrawal of the drug only.

GEIGY COMPANY, INC.

Tablets Tromexan Ethyl Acetate: 0.15 Gm. and 0.3 Gm.

U. S. patents 2,482,510, 2,482,511 and 2,482,512.

**HEPARIN SODIUM-U.S.P.—Liquaemin Sodium (ORGANON).—**“Heparin Sodium is a mixture of active principles, having the property of prolonging the clotting time of blood in man or other animal. It is usually obtained from the livers or lungs of domesticated mammals used for food by man.

“Heparin Sodium exhibits a potency not less than 90 per cent and not more than 110 per cent of the potency stated on the label, which labeled potency is not less than 100 U.S.P. Heparin Units per milligram.”

**Physical Properties.**—Heparin sodium is a white or pale-colored, amorphous powder. It is odorless, or nearly so, and is hygroscopic. One gram of heparin sodium dissolves in 20 cc. of water.

**Actions and Uses.**—Heparin sodium inhibits blood coagulation. It may aid the normal body to maintain the fluid state of the blood as traces are detectable in the blood. Very little is known concerning the metabolism, excretion and fate of heparin sodium in the body. Its anticoagulant action appears to be effected by action on the thrombin.

Heparin sodium is of value as a substitute for citrate in blood transfusions, in attempts to prevent postoperative thrombosis and possibly thrombosis of other origin, to prevent recurring thrombosis in phlebitis and pulmonary embolism, to initiate the rapid action of anticoagulant therapy in vascular surgery and for other uses.

**Dosage.**—The potency of heparin sodium is expressed in terms of U.S.P. units because variations in dosage are possible when potency is declared only on the basis of weight. Until sufficient purification has been achieved to permit uniform declaration of potency in terms of weight, products should be labeled only in terms of the official units. Dosages stated below in terms of weight are based upon the U.S.P. *minimum* potency of 100 units per milligram.

The substance is inactive orally or sublingually and is usually injected intravenously or intramuscularly. It may be given by single



injection or continuous intravenous drip, the infusion being adjusted by watching the coagulation time. The clotting time should be maintained between 15 and 20 minutes. If a chill develops or spontaneous bleeding occurs, the drug should be stopped. When the interrupted dose method is employed, 5,000 units (50 mg.) may be administered at intervals of 4 hours up to a total of 25,000 units (250 mg.) per day. For continuous drip, 10,000 (100 mg.) to 20,000 units (200 mg.) is added to 1,000 cc. of 5 per cent sterile dextrose or isotonic sodium chloride solution. The flow may be started at about 20 drops per minute.

Heparin sodium in aqueous solution may also be administered by intramuscular or deep subcutaneous injection, but the possibility of local hematoma or tissue irritation must be kept in mind. The possibility of concealed serious hemorrhage from accidental puncture of a blood vessel following deep injection into the tissues should also be kept in mind. This disadvantage can be minimized by administering the heparin subcutaneously with a hypodermic needle (25 or 26 gage) in more concentrated solutions. Solutions containing 5,000 units (50 mg.), 10,000 units (100 mg.) or 20,000 units (200 mg.) per cubic centimeter may be injected into the tissues in doses of 10,000 units (100 mg.) to 12,000 units (120 mg.) every 8 hours or 14,000 units (140 mg.) to 20,000 units (200 mg.) every 12 hours. Solutions of this concentration also are suitable for use without dilution for intermittent intravenous injection.

Prolonged anticoagulant action of the drug is provided by deep subcutaneous or intramuscular injection of repository dosage forms prepared with a vehicle of gelatin and dextrose with and without added vasoconstrictors. Both forms are used simultaneously in equal amounts (except that when vasoconstrictors are contraindicated, only the latter is used) to provide a total initial dose of 0.3 to 0.4 Gm. of the drug, administered by deep subcutaneous injection in the thigh or buttocks. At the end of 12 hours, the clotting time should be checked by the Lee-White method. If found to be shorter than 20 minutes, 0.2 Gm. of the drug should be administered; if longer than 20 minutes, the next dose should be deferred until clotting time is shorter than 20 minutes. In some patients this may be found to occur within 10 hours; in others, it may require 16 hours or longer. After a few such trials, the average response will be determined. It is always safest to determine the clotting time before more heparin sodium is administered. Maintenance of the blood coagulation time at 30 to 60 minutes is adequate elevation. As a rule, coagulation time should be not less than three times as great as it was at the start of therapy.

#### ABBOTT LABORATORIES

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent phenol.

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. 5 cc. vials. A solution containing 10,000



U.S.P. units (approximately 100 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

#### ORGANON, INCORPORATED

**Solution Liquaemin Sodium:** 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.45 per cent phenol.

**Solution Liquaemin Sodium (*High Potency*):** 1 cc. ampuls and 10 cc. vials. A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.45 per cent phenol.

**Solution Liquaemin Sodium (*Extra High Potency*):** 2 cc. vials. A solution containing 20,000 U.S.P. units (approximately 200 mg.) of heparin sodium in each cubic centimeter. Preserved with thimerosal 1:10,000.

U. S. trademark 361,309.

#### PREMO PHARMACEUTICAL LABORATORIES, INC.

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.45 per cent phenol.

#### TESTAGAR & COMPANY, INC.

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent phenol.

**Solution Heparin Sodium (*High Potency*):** 10 cc. vials. A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent phenol.

#### THE UPJOHN COMPANY

**Depo-Solution Heparin Sodium:** 1 cc. cartridges. A solution containing 20,000 U.S.P. units (approximately 200 mg.) of heparin sodium in each cubic centimeter. Preserved with thimerosal 1:10,000.

U. S. trademark 515,760 (Depo).

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

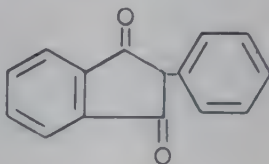
**Solution Heparin Sodium:** 4 cc. vials. A solution containing 10,000 U.S.P. units (approximately 100 mg.) of heparin sodium in each cubic centimeter. Preserved with 5 mg. of chlorobutanol.

## WALKER LABORATORIES, INC.

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 1,000 U.S.P. units (approximately 10 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Solution Heparin Sodium:** 10 cc. vials. A solution containing 5,000 U.S.P. units (approximately 50 mg.) of heparin sodium in each cubic centimeter. Preserved with 0.45 per cent phenol.

**PHENINDIONE.**—Danilone (SCHIEFFELIN).—Hedulin (WALKER).—2-Phenyl-1,3-indandione.—The structural formula of phenindione may be represented as follows:



**Physical Properties.**—Phenindione is a pale yellow, crystalline material, which is practically odorless. It is very slightly soluble in water. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 1 Gm. in alcohol and 0.9 Gm. in ether.

**Actions and Uses.**—Phenindione, a synthetic anticoagulant, is similar in action to bishydroxycoumarin and its derivatives but is chemically unrelated. It is effective orally for lowering of the blood concentration of thrombin in the management of conditions characterized or complicated by intravascular clotting. (See the monographs on bishydroxycoumarin, cyclocumarol and ethyl biscoumacetate.)

Phenindione acts more promptly than does bishydroxycoumarin and is effective in smaller doses. Therapeutic levels are usually obtained within 18 to 24 hours following the institution of therapy. Cumulative effects have not been observed, and the prothrombin time of the blood usually returns to normal within 24 to 48 hours after the drug is discontinued. As an anticoagulant the agent is thus considered to be relatively safe. However, the predictability and controllability of its effect is not considered superior to other short-acting oral anticoagulants.

As with all systemic anticoagulants, the drug should not be given to patients with a hemorrhagic tendency, such as hemophilia, thrombocytopenic purpura and leukemia with pronounced bleeding tendency, or to patients with open wounds or ulcerations, particularly of the gastro-intestinal tract.

**Dosage.**—Phenindione is administered orally. The initial total daily dosage should be 0.2 to 0.3 Gm., half given in the morning and half at bedtime. Patients weighing less than 70 Kg. should be given 0.2 Gm. daily; those weighing more than 70 Kg. should receive 0.3 Gm. daily. This usually does not result in excessive lowering of the blood prothrombin level, but subsequent dosage is subject to adjustment in accordance with prothrombin time deter-

minations. Maintenance dosage should be adjusted to lengthen the prothrombin time from two to two and one-half of normal values. The maintenance dosage may vary from 0.05 to 0.1 Gm. per day, given in the same manner as the initial dose. The average maintenance dose is approximately 75 mg. When this has been established by daily prothrombin determinations for the first 3 days, the tests for prothrombin time need be repeated only at 7 to 14 day intervals or as may be indicated by the patient's response. If hemorrhage occurs, the drug should be withdrawn immediately and, when necessary, 50 to 75 mg. of vitamin K should be administered intravenously with or without transfusions of fresh whole blood or plasma.

GANE'S CHEMICAL WORKS, INC.

Powder Phenindione: Bulk; for manufacturing use.

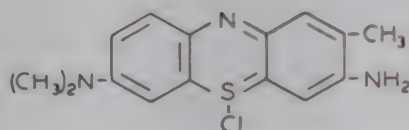
SCHIEFFELIN & COMPANY

Tablets Danilone: 50 mg.

WALKER LABORATORIES, INC.

Tablets Hedulin: 50 mg.

**TOLONIUM CHLORIDE.**—**Blutene Chloride** (ABBOTT).—3-Amino-7-dimethylamino-2-methylphenazothionium chloride.—The structural formula of tolonium chloride may be represented as follows:



**Physical Properties.**—Tolonium chloride is a green, crystalline powder with a bronze luster. It is slightly soluble in alcohol, very slightly soluble in chloroform and practically insoluble in ether. The amount which dissolves at 25° in water to form 100 ml. of solution is about 5.5 Gm.

**Actions and Uses.**—Tolonium chloride, known as a dye by the name of toluidine blue O, exhibits in vitro antiheparin activity. In animals the coagulation times of blood samples known to contain an excess of heparin can be returned to normal by the addition of small amounts of the dye. Clinically, the systemic administration of the dye reduces the bleeding tendency in certain hemorrhagic conditions associated with excessive amounts of heparinoid substances in the blood. An excess of these substances can be determined by a simplified method of protamine titration using protamine sulfate, a known antiheparin compound. A protamine sulfate titration value of 0.14 mg. is considered the upper limit of normal.

Tolonium chloride is useful in the treatment of idiopathic functional uterine bleeding: menorrhagia or hypermenorrhea (abnormally profuse or prolonged menstruation) and menometror-



rhagia (excessive or prolonged menstruation and intermenstrual bleeding). Approximately 80 per cent of patients with idiopathic uterine bleeding have elevated protamine titration values, and 75 to 80 per cent of the patients in this category respond to the dye. In patients treated empirically (not selected on the basis of elevated protamine values), the dye reduces bleeding in about 65 per cent. The mechanism of action has not been explained in uterine bleeding not associated with elevated protamine titration that responds to the dye. The dye should not be employed for the treatment of abnormal uterine bleeding until adequate examination and study have ruled out malignancy as the cause and, when so used without protamine titration, only if all other organic diseases have been ruled out.

Tolonium chloride has been demonstrated to have a low order of toxicity in experimental animals; no changes in coagulation time or capillary fragility have been observed. Extremely high doses injected into dogs produce hemolysis, leukocytosis and thrombosis, but these effects have not been encountered with therapeutic doses in man. Staining of internal organs may be apparent for a period of time following systemic administration of the dye, but no tissue damage has been attributed to this effect. The urine of patients receiving treatment becomes pale blue-green. Therapy also may be associated with such side effects as nausea, burning on urination and tenesmus, but these are usually absent or minor in importance in patients consuming adequate fluids. Since the side effects may respond to increased fluid intake, decreased dosage, or both, it is rarely necessary to discontinue therapy.

**Dosage.**—Tolonium chloride is administered orally. The usual dosage is between 0.2 and 0.3 Gm. daily. For the treatment of menorrhagia, 0.2 to 0.3 Gm. is administered with meals during the menstrual period; for the prevention of menorrhagia, the same daily dosage is administered for 5 or 6 days prior to the estimated time of the menses. In menometrorrhagia, medication may be extended over two or three menstrual periods.

ABBOTT LABORATORIES

Tablets Blutene Chloride: 100 mg.

## HEMOSTATICS

**ABSORBABLE GELATIN SPONGE-U.S.P.—Gelfoam (UPJOHN).**—“Absorbable Gelatin Sponge is a sterile, absorbable, water-insoluble gelatin-base sponge.” *U.S.P.*

**Physical Properties.**—Absorbable gelatin sponge is a light, nearly white, nonelastic, tough, porous matrix. It shows no tendency to disintegrate even with relatively rough handling. A piece of absorbable gelatin sponge may be wetted rapidly by kneading it vigorously with moistened fingers. A 10-mm. cube of absorbable gelatin sponge weighing approximately 9 mg. will take up approximately 50 times its weight of water or 45 times its weight of well-agitated oxalated whole blood. Absorbable gelatin sponge will withstand dry heat at 149° for 4 hours.

It is insoluble in aqueous media but is absorbable in body tissues. It is completely digested by a solution of pepsin.

**Actions and Uses.**—Absorbable gelatin sponge material, although insoluble in aqueous mediums, is absorbable and therefore may be used as a surgical sponge which may be left in place following closure of an operative wound. This material will be completely absorbed in 4 to 6 weeks without inducing excessive formation of scar tissue or excessive cellular reaction. It is indicated in the control of capillary bleeding, particularly when moistened with thrombin solution.

**Dosage.**—Absorbable gelatin sponge may be applied to the bleeding surfaces in amounts sufficient to cover the area. For such purposes it should first be moistened thoroughly with sterile isotonic sodium chloride solution or thrombin solution.

#### THE UPJOHN COMPANY

**Sponge Gelfoam:** Box of four sponges in individual envelopes and jars containing four sterile sections 20 by 60 mm., and sterile envelopes containing a single section 80 by 125 mm.

U. S. patent 2,465,357.

**CYANOCOBALAMIN.**—See the monograph in the chapter on vitamins.

**FIBRIN FOAM.**—A sterile, dry preparation of fibrin prepared from Fraction I of citrated normal human plasma as fractionated by the method of Cohn (*J. Am. Chem. Soc.* 68:459, 1946). It complies with the requirements of the National Institutes of Health of the United States Public Health Service.

**Physical Properties.**—Fibrin foam (human) consists of small, yellowish, rectangular, fragile, sponge-like pieces which become compressible and resilient when completely wetted with water.

**Actions and Uses.**—Fibrin foam (human) acts as a mechanical coagulant, and in combination with thrombin gives a chemical as well as a mechanical matrix for coagulation. It has been used in surgery of the brain, liver, kidneys and other organs where ordinary methods of hemostasis are ineffective or inadvisable.

**Dosage.**—Fibrin foam is applied directly to the oozing surface.

#### CUTTER LABORATORIES

**Fibrin Foam and Thrombin (Human):** Packages containing a 250 mg. (6.25 to 12.55 cc.) jar of fibrin foam, a vial of thrombin (human) containing not less than 200 units, and a 20 cc. vial of isotonic sodium chloride solution.

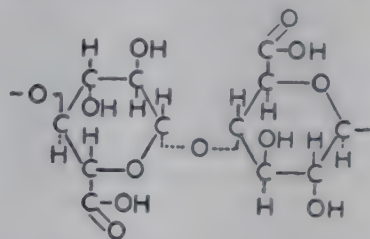
The thrombin supplied meets the requirements of the National Institutes of Health of the United States Public Health Service and is derived from human plasma.

Licensed by Research Corporation under U. S. patent 2,389,074.

**OXIDIZED CELLULOSE-U.S.P.—Oxycel (PARKE, DAVIS).**—Absorbable cotton or gauze.—Cellulosic acid.—“Oxidized Cellulose, dried in a vacuum over phosphorous pentoxide for 18 hours, contains not less than 16 per cent and not more than 24 per cent of



carboxyl groups ( $-\text{COOH}$ ).” *U.S.P.* The accepted structural formula for cellulosic acid may be represented as follows:



**Physical Properties.**—Oxidized cellulose, in the form of gauze or cotton, is almost white in color. It has an acid taste and a slight, charred odor. It is soluble in dilute alkalis but insoluble in acids and in water.

**Actions and Uses.**—Oxidized cellulose, a specially treated form of surgical gauze or cotton, exerts an unusual hemostatic effect and is absorbable when buried in the tissues. Its hemostatic action depends on the formation of an artificial clot by cellulosic acid. This acid has a marked affinity for hemoglobin, but does not enter per se into the physiologic mechanism of clotting. Absorbability depends on the size of the implant used, the adequacy of the blood supply to the area and the degree of chemical degradation of the material. Absorption of oxidized cellulose occurs between the second and seventh day following implantation of the dry material, but complete absorption of large amounts of blood-soaked material may take 6 weeks or longer.

Oxidized cellulose is valuable in surgery for the control of moderate bleeding under conditions where suturing or ligation is technically impractical or ineffective. Such situations include the control of capillary, venous or small arterial hemorrhage encountered in operations upon the biliary tract, partial hepatectomy, resections or injuries of the pancreas, spleen or kidneys, bowel resections, amputations, resections of the breast, thyroid and prostate and in certain aspects of neurologic and otolaryngologic surgery. Oxidized gauze is employed as a sutured implant or temporary packing depending on the anatomic site or structures involved. When employed as uterine packing it should be used only in severe postpartum hemorrhage. Oxidized cotton is used primarily for neurologic surgery as unsutured packing, small portions of which may be allowed to remain inside when the wound is closed to control small areas of oozing from the dura or brain tissue. This material is likewise useful as temporary packing for control of secondary hemorrhage following adenoidectomy, tonsillectomy and other oral procedures and for control of alveolar bleeding following tooth extraction. Neither oxidized gauze nor oxidized cotton should be used for permanent packing or implantation in fractures because it interferes with bony regeneration and may result in cyst formation.

The hemostatic action of oxidized cellulose is not enhanced by the addition of other hemostatic agents. Thrombin would be de-



stroyed by the low pH of the material and the hemostatic action of either alone is greater than that of the combination. Moistening with water or saline is not recommended, as the hemostatic effect is greater when the dry material is applied. When properly used, oxidized cellulose may be closed in a clean wound without drainage, but this is hazardous whenever gross contamination is suspected or frank infection is present.

*Neither oxidized gauze nor oxidized cotton should be used as a surface dressing except for the immediate control of hemorrhage, as cellulosic acid inhibits epithelialization.*

**Dosage.**—The amount of oxidized gauze or cotton used varies with the circumstances. As a rule, only the minimal amount required to control hemorrhage should be used. For the control of hemorrhage from the prostatic bed, this may vary from one to four 2 inch by 14 inch gauze packing strips, depending upon the extent and vascularity of the area to be packed and the technic employed. This size of oxidized gauze is particularly designed for implantation by means of mattress sutures. Gauze packing strips  $\frac{1}{2}$  inch by  $2\frac{1}{2}$  yards are adapted for otolaryngologic or dental procedures; gauze packing 2 inches by 3 yards (4 ply) is used for severe postpartum uterine hemorrhage; cotton pads, 2 inches by 6 inches, are designed for neurologic, oral and/or dental surgical procedures.

In the event that it is desired to remove gauze or cotton from a hollow viscus or drainage site before dissolution is complete, removal can be facilitated by irrigation. Discs of gauze may be used in conjunction with hemostatic bags to control hemorrhage following suprapubic or retropubic prostatectomy.

#### PARKE, DAVIS & COMPANY

**Oxycel Cotton Pledgets:**  $2\frac{1}{4}$  inches by 1 inch by 1 inch in a glass vial.

**Oxycel Gauze Discs (Foley Cones) (4 ply):** 5 inches and 7 inches each in a glass vial.

**Oxycel Gauze Pads (8 ply):** 3 inches by 3 inches in a glass vial.

**Oxycel Gauze Strips (4 ply):** 18 inches by 2 inches in a glass vial.  
U. S. trademark 410,383.

**THROMBIN-U.S.P.**—"Thrombin is a sterile protein substance prepared from prothrombin of mammalian origin through interaction with added thromboplastin in the presence of calcium. It is capable of accelerating the clotting of blood. The prothrombin is usually of human or bovine origin. Thrombin complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Physical Properties.**—Thrombin is a white or grayish, amorphous substance dried from the frozen state.

**Actions and Uses.**—Thrombin is intended as a hemostatic for topical application to control capillary bleeding in operative procedures. It may be applied as a dry powder or dissolved in sterile, isotonic saline solution. *It should never be injected.*

**Dosage.**—Thrombin is applied as a dry powder or in solutions containing 1,000 to 5,000 thrombin units.

**PARKE, DAVIS & COMPANY**

**Thrombin Topical (*Bovine Origin*):** Each vial contains 1,000 units of thrombin topical. Preserved with 0.04 mg. of benzethonium chloride. Three vials packaged with one 6 cc. vial of isotonic sodium chloride diluent, preserved with benzethonium chloride 1:50,000.

**Thrombin Topical (*Bovine Origin*):** 5,000 units. Each ampul contains 5,000 units of thrombin and sucrose, packaged with a 5 cc. vial of sterile isotonic saline solution preserved with 0.1 mg. of benzethonium chloride.

U. S. patent 2,398,077

**THE UPJOHN COMPANY**

**Thrombin Topical (*Bovine Origin*):** 30 cc. vials. Each vial contains 1,000 or 5,000 units of dried thrombin.

## Cardiovascular Agents

Cardiovascular agents are those whose action on the heart and other muscular portions of the vascular system is such as to affect either the total output of the heart or the distribution of blood to particular branches of the circulation. Accordingly, this chapter deals with (1) drugs which primarily affect the rhythm and output of the heart and (2) vasodilator agents.

The vasoconstrictor agents, such as epinephrine, will be found in the chapter on autonomic drugs, while ergot preparations are described in the chapter on oxytocics. A number of drugs with less definite vasodilator effects are described in other chapters; theobromine, caffeine and other xanthine derivatives in the chapter on diuretics, caffeine again in the chapter on central nervous system depressants and stimulants.

### DIGITALIS AND RELATED PRINCIPLES

The digitalis group embraces many crude drugs and proximate principles which have a peculiar action on cardiac muscle. We are best informed concerning the actions of digitalis, strophanthus and squill.

All preparations of digitalis and related principles act directly on heart muscle. They diminish the size of the heart as measured by the x-ray silhouette. While they increase the output of diseased hearts, they diminish that of normal hearts. The margin between therapeutic and toxic actions on the heart differs for different substances, although the margin of safety is the same. In patients with auricular fibrillation these drugs all slow the heart rate by a combination of a direct action on the heart muscle and indirect inhibition by stimulation of the vagus. The larger the dose, the more pronounced is the direct action. The proportion of these two actions is similar in all members of the group.

Differences between the drugs occur chiefly in absorption from the gastro-intestinal tract, speed of elimination and local emetic action. Their potencies differ, and difficulties arise because the biologic methods of standardization are crude.

*Differences in Absorption.*—Digitalis contains a mixture of glycosides, some of which are rapidly, and others poorly absorbed from the gastro-intestinal tract. After an oral dose only about one-fifth of the potent materials produce a systemic action, as shown by the fact that it requires only about one-fifth as much for intravenous as for oral administration to produce the same results. The potent



principles of strophanthus are so poorly absorbed from the gastro-intestinal tract that they are undesirable for oral administration and are used chiefly by intramuscular or intravenous injection in small doses.

**Differences in Cumulative Action.**—All the digitalis bodies in common use are cumulative in action. Not all show the same degree of cumulation, however, since some are more rapidly eliminated than others. The cumulative action is especially pronounced with digitalis leaf and digitoxin. It is much less with strophanthus and strophanthin. Gitalin (amorphous) is less cumulative than digitoxin, but more so than digoxin, ouabain and most tinctures of digitalis.

**Differences in Emetic Action.**—The digitalis principles are irritant to mucous membranes and subcutaneous tissues. Large doses produce in the gastro-intestinal tract the local irritation which may be sufficient to cause nausea and vomiting within several minutes to one or two hours. These drugs, however, are rarely administered in such doses, and when given in the usual smaller doses the local irritant action is insufficient to cause nausea or vomiting. The nausea or vomiting which follows the customary doses of digitalis is due to a systemic action after absorption and represents a toxic symptom. The seat of this action is the vomiting center which is affected indirectly through the heart. The emetic action is roughly proportional to the cardiac effects of the various members of the group and when this undesired action is induced, it cannot be avoided by changing the mode of administration or by resorting to other members of the group. In such a case, the patient is overdigitalized and the size of the dose should be reduced.

**Standardization.**—There are various methods for the standardization of this group of drugs, involving the use of several species of animals, such as the frog, guinea pig and pigeon. The *U. S. Pharmacopeia* requires that digitalis be standardized against the U.S.P. Digitalis Reference Standard by the official pigeon method which involves intravenous injection into pigeons until death occurs by cardiac arrest. The Standard preparation and the unknown are injected into groups of birds and the average fatal doses of the two are compared. The unknown is then adjusted so that 0.1 Gm. has the potency of 0.1 Gm. of the Standard, or 1 U.S.P. Digitalis Unit. Since the U.S.P. Digitalis Unit is the result of an assay by the pigeon method and represents an improved technic in bioassay, the expression of potency in U.S.P. Digitalis Units is preferable to the older expression in terms of "cat units." By direct testing it has been found that 1 U.S.P. Digitalis Unit is equivalent approximately to 1.3 "cat units," using the cat method of assay.

For digitalis leaf and tincture, the results of comparison by means of assays agree with similar comparisons in human beings to whom the drugs are given orally, but there is less agreement on purified materials because of wide differences in their absorption from the gastro-intestinal tract, and because the intravenous method does not distinguish absorbable from nonabsorbable material. Hence U.S.P. units of different specimens of the Digitalis Leaf or Tincture Digitalis produce similar results when given

orally to man (although there are some exceptions), but U.S.P. units of purified materials do not.

The purified oral preparations provide the active glycosides in a form more readily absorbable than do the whole leaf preparations. This difference in absorption is responsible for 20 to 30 per cent greater clinical effect from these preparations than from crude digitalis preparations of equal strength.

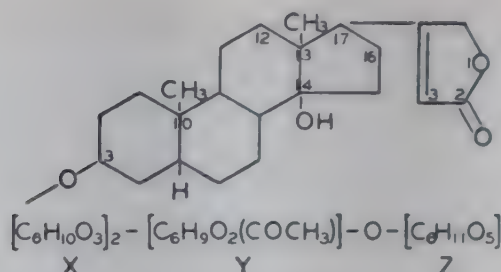
Digitalis and digitalislike principles may be administered by mouth, by injection or as described under the accepted preparations. The *U. S. Pharmacopeia* recognizes a solution of digitalis for injection, but the optimum frequency of the intravenous dose of different digitalis preparations varies widely, even with those of equal potency, depending particularly on difference in persistence of action. The physician must learn the proper intravenous dosage of any preparation of digitalis which he employs. In general, the intravenous use of digitalis is seldom needed; other methods of administration are generally safer and equally effective.

**Research.**—The disadvantages of all the drugs of the digitalis group have served as a constant stimulus in the search for pure principles suitable for intramuscular or intravenous administration. Pure principles would obviate the necessity of biologic standardization. A potent pure principle which is completely absorbed from the gastro-intestinal tract would make it possible to digitalize rapidly by oral administration without the danger of local irritant action of the large amount of nonabsorbable glycosides. Several glycosides are available in a high degree of purity, such as strophanthin, ouabain, digitoxin, digoxin and lanatoside C. Many preparations, such as digifolin or digalen, however, are mixtures of glycosidal materials.

**Proprietary Digitalis Preparations.**—Several digitalis preparations have been introduced into therapeutic use with the claim that they are composed either of pure principles or of purified extracts of digitalis, and that they are devoid of certain disadvantages of the preparations of the *U. S. Pharmacopeia*. The Council recommends that clinicians acquire skill in the use of a few digitalis materials rather than attempt to use without discrimination the large number of preparations which are offered.

**DIGILANID.** — A mixture of the isomorphous crystallized cardio-active glycosides, lanatoside-A ( $C_{49}H_{76}O_{19}$ ), lanatoside-B ( $C_{49}H_{76}O_{20}$ ) and lanatoside-C ( $C_{49}H_{76}O_{20}$ ), obtained from *Digitalis lanata* by extracting the wet leaves with ethyl acetate. The extract is purified by selective precipitation procedures and subsequently recrystallized from dilute methyl alcohol. The three components are present in the mixture in the proportions in which they occur in the crude drug, namely, about 47 per cent lanatoside-A, 16 per cent lanatoside-B and 37 per cent lanatoside-C. The structural formula of lanatoside-A, as far as it is known, is represented here. In this formula X = digitoxose, Y = acetyldigitoxose and Z = glucose. Lanatoside-B and lanatoside-C differ from lanatoside-A in having a hydroxyl group attached to carbon atoms 16 and 12, respectively.





**Physical Properties.**—The air-dried mixture is a white, odorless powder with a bitter taste. When heated rapidly, this preparation melts with decomposition above 245°. It is soluble in 20 parts of methanol and in 10,000 parts of water and is insoluble in ether.

**Actions and Uses.**—The actions and uses are closely similar to those of digitalis. (See the general statement on digitalis and related principles.)

**Dosage.**—The usual method of treatment is to give 0.67 to 1.33 mg. daily in tablet form, until the desired therapeutic effects are induced. The dose is then reduced to the maintenance level: 0.33 to 0.67 mg. daily in tablet form. (When digitalis effects are urgently needed, it may be desirable to initiate treatment with larger oral doses or with intramuscular or intravenous injections.) For rapid parenteral digitalization, 0.8 mg. (4 cc.) by cautious intravenous injection, or 0.4 mg. (2 cc.) twice daily by intramuscular injection. Rectally, 0.5 to 1 mg. (1 or 2 suppositories) daily, as required.

The same precautions should be observed as when giving any digitalis preparation.

#### SANDOZ CHEMICAL WORKS, INC.

**Solution Digilanid:** 2 cc. and 4 cc. ampuls. A solution in alcohol, glycerin and water containing 0.2 mg. of digilanid in each cubic centimeter.

**Solution Digilanid (Oral):** 30 cc. and 90 cc. vials. A solution in alcohol, glycerin and water containing 0.33 mg. of digilanid in each cubic centimeter.

**Suppositories Digilanid:** 0.5 mg.

**Tablets Digilanid:** 0.33 mg.

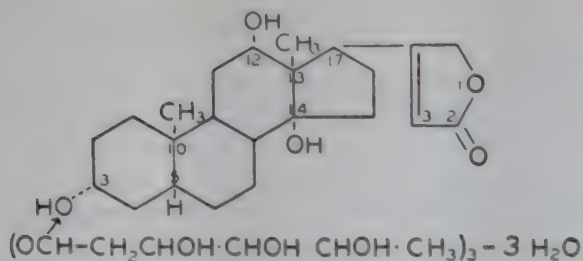
U. S. trademark 291,301.

**DIGOXIN-U.S.P.**—"Digoxin is a glycoside obtained from the leaves of *Digitalis lanata*, Ehrh. (Fam. *Scrophylariaceae*)."  
U.S.P.

The crude lanatosides from the leaves are separated by physical methods into lanatosides A, B and C. Digoxin is formed from lanatoside-C by hydrolytic removal of acetyl and glucose groups. The potency of digoxin corresponds to the potency of an equal weight of U.S.P. Digoxin Reference Standard.

The structural formula of digoxin, as far as it is known, may be represented as follows, where the sugar attached at position 3 is digitoxose:





**Physical Properties.**—Digoxin occurs as colorless to white crystals or as a white, crystalline powder. It is odorless and melts indistinctly and with decomposition at about  $235^\circ$ . It is insoluble in water, in chloroform and in ether. It is freely soluble in pyridine and soluble in dilute alcohol.

**Actions and Uses.**—The actions and uses of digoxin are similar to those of digitalis-U.S.P. Because it is a purified substance it has particular usefulness when rapid digitalization is desired. Its action is manifest usually within a few hours when administered orally and within a few minutes when administered intravenously. (See the general statement on digitalis and related principles.)

**Dosage.**—Large doses of digoxin should not be administered if any of the digitalis group has been given within 2 weeks.

For rapid digitalization by the oral route, an initial dose of 0.75 to 1.5 mg. may be administered, followed by doses of 0.25 to 0.75 mg. at 6-hour intervals until, if auricular fibrillation is present, the ventricular rate lies between 60 and 70 or the maximum therapeutic effect is obtained or toxic symptoms appear.

If the patient has had no drugs of the digitalis group within 2 weeks, very rapid digitalization may be accomplished with an intravenous injection of 0.75 to 1 mg. If auricular fibrillation is present, ventricular slowing usually begins within a few minutes and is maximal in 1 to 2 hours. If complete digitalization is not obtained after 6 hours, additional doses of 0.25 to 0.5 mg. of digoxin may be given intravenously at 6-hour intervals.

For maintenance, 0.25 to 0.75 mg. may be given daily by mouth, or 0.25 to 0.5 mg. by intravenous injection.

Digoxin injection is a tissue irritant and the contents of the ampul should be diluted with 10 cc. of sterile isotonic solution. The product should be injected slowly (5 to 10 minutes) and care taken to avoid extraveneous injection.

**"Caution—Digoxin is extremely poisonous." U.S.P.**

BURROUGHS WELLCOME & COMPANY, INC.

**Solution Digoxin, 0.05%:** 1 cc. ampuls. A 70 per cent alcohol solution containing 0.5 mg. of digoxin in each cubic centimeter.

**Tabloid Digoxin: 0.25 mg.**

U. S. trademark 76,731 (Tabloid).

**GITALIN (AMORPHOUS).**—Gitaligin (WHITE).—A glycosidal constituent of *Digitalis purpurea* Linné prepared according to the method of Kraft. Dried and ground leaves are extracted with cold

water and the extract is then purified by selective precipitation and extraction technics.

**Physical Properties.**—Gitalin (amorphous) is a white or pale buff, amorphous powder which melts with decomposition between 110 and 150°. It is readily soluble in acetone, alcohol, chloroform and ether, slowly soluble in 600 parts of water and insoluble in carbon disulfide and petroleum ether. A saturated aqueous solution is neutral to litmus and has an intensely bitter taste.

**Actions and Uses.**—Gitalin (amorphous), a mixture of digitalis glycosides, has the same action and uses as digitalis itself. The rate of elimination or destruction is slower than that of digoxin but more rapid than that of digitoxin. Several investigations made in the clinic have suggested that the drug may have a more favorable ratio of therapeutic to toxic properties than other digitalis preparations, though only prolonged experience can finally determine this fact. (See the general statement on digitalis and related principles.)

**Dosage.**—Gitalin (amorphous) is administered orally. For initial digitalization when rapid effects are desired, an initial dose of 2.5 mg. is followed by 0.75 mg. every 6 hours until a total of approximately 6 mg. has been given or until the full effect is manifested by toxic signs; when slower effects are adequate, a daily dose of 1.5 mg. is given for 4 to 6 days. The foregoing schedules apply only when the patient has had no digitalis or related drug for at least 2 weeks prior to the initiation of digitalization. For maintenance, the average dose is 0.5 mg. daily, preferably administered in the morning; occasionally a daily dose as low as 0.25 mg. or as high as 1.25 mg. is necessary for proper maintenance. As with all other digitalis preparations, constant supervision is essential to avoid the toxic effects of overdigitalization.

WHITE LABORATORIES, INC.

Tablets Gitaligin: 0.5 mg.

**URGININ.**—A mixture containing equal weights of two water-insoluble glycosides, Uarginin A and Uarginin B, derived from the dried bulbs of squill, *Urginea maritima*.

**Physical Properties.**—Uarginin is a yellow powder with a slight characteristic odor and an extremely bitter taste. It is soluble in alcohol and acetone, sparingly soluble in chloroform and practically insoluble in water and ether. A saturated aqueous solution is neutral to litmus.

**Actions and Uses.**—The cardiac action of uarginin is essentially similar to that of digitalis. (See the general statement on digitalis and related principles.)

**Dosage.**—In cardiac decompensation, when digitalis has not been used within 2 weeks, 3 mg. may be given daily in divided doses at intervals of 6 hours, until the usual effects of the drug are observed, after which the maintenance dose of 0.5 mg. to 1 mg. may be given. Overdosage of uarginin may produce nausea. The first symptom of nausea indicates a reduction in the amount and or frequency of administration.



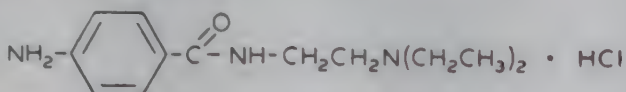
GRISARD LABORATORIES

Tablets Uarginin: 0.5 mg.

U. S. patent 1,972,876. U. S. trademark 324,695.

## HEART MUSCLE DEPRESSANTS

**PROCAINE AMIDE HYDROCHLORIDE.**—**Pronestyl Hydrochloride** (SQUIBB). — *p*-Amino-N-(2-diethylaminoethyl)benzamide hydrochloride.—The structural formula of procaine amide hydrochloride may be represented as follows:



**Physical Properties.**—Procaine amide hydrochloride is a white to tan, odorless, crystalline solid. It melts between 165 and 169°. It is very soluble in water, soluble in alcohol, slightly soluble in chloroform and very slightly soluble in benzene and ether.

**Actions and Uses.**—Procaine amide hydrochloride, like procaine hydrochloride, depresses the irritability of the ventricular muscle. Unlike the latter, procaine amide is only slightly hydrolyzed by plasma enzymes to *p*-aminobenzoic acid and diethylaminoethylamine so that its effect is more prolonged. Procaine amide is tolerated in larger intravenous doses than is procaine; on a weight basis, the amide is about one-half to two-thirds less toxic. It differs from procaine also in that it does not produce significant central stimulatory effects. The action occurs almost immediately after intravenous administration and the plasma level declines about 10 to 15 per cent per hour; after oral administration therapeutic levels are attained within 30 minutes to one hour. Plasma levels and urinary excretion rates following oral administration are comparable to those following intravenous injection, indicating almost complete absorption of the drug by the gastro-intestinal tract. About 60 per cent is excreted unchanged; some is probably hydrolyzed as indicated above; the fate of the remainder is unknown.

Procaine amide hydrochloride is useful for the treatment of ventricular and auricular arrhythmias and extrasystoles occurring either in cardiac diseases or during general anesthesia. When administered intravenously the drug produces a hypotensive effect which is less severe than that with procaine; this effect is partially due to vasodilatation. Hypotensive reactions may be precipitous and clinical judgment is required to determine whether it is necessary to administer vasoconstrictor agents or to discontinue therapy. Epinephrine is likely to aggravate an existing arrhythmia and is therefore generally contraindicated during cyclopropane anesthesia. Until more conclusive evidence becomes available procaine amide hydrochloride is not recommended for the prevention of cardiac arrhythmias, anticipated in either conscious or unconscious subjects.

Leukopenia and granulocytopenia have followed the repeated



use of the drug, so that it is imperative to obtain a blood count at regular intervals and to instruct patients to report promptly symptoms indicating the possible development of agranulocytosis. The drug should be promptly discontinued when such symptoms are accompanied by a significant reduction in the white blood cell count.

**Dosage.**—In conscious patients for the treatment of ventricular tachycardia, 1 Gm. is given orally, followed by 0.5 to 1 Gm. every 4 to 6 hours as indicated, or 0.2 to 1 Gm. (2 to 10 cc. of a solution containing 100 mg. in each cubic centimeter) administered intravenously at a rate not greater than 1 cc. per minute. For the treatment of auricular arrhythmias, the total daily oral dose ranges from 1 to 5 Gm. given in three or four divided doses. Initially 1.25 Gm. may be given, followed by 0.75 Gm. if there are no electrocardiographic changes. Several further doses of 0.5 to 1 Gm. may then be given every 2 hours until the auricular arrhythmia is eliminated. A maintenance dose of 0.5 to 1 Gm. every 3 to 6 hours is suggested. The intravenous dose averages 0.5 Gm., although up to 1 Gm. is sometimes given. For the treatment of runs of ventricular extrasystoles, 0.5 Gm. is given orally every 4 to 6 hours as indicated. During anesthesia, 0.1 to 0.5 Gm. is administered intravenously at a rate not greater than 0.2 Gm. (2 cc.) per minute.

Occasional transient electrocardiographic changes resembling those of quinidine intoxication have been observed with procaine amide hydrochloride. Intravenous injection is subject to the danger of hypotensive action; oral administration is not.

**E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION**

**Capsules Pronestyl Hydrochloride:** 0.25 Gm.

**Solution Pronestyl Hydrochloride:** 10 cc. vials. A solution containing 100 mg. of procaine amide hydrochloride in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol and 0.09 per cent sodium bisulfite.

U. S. trademark 557,523.

## **HYPOTENSIVE AGENTS**

In this group of agents are included those preparations used primarily for the treatment of essential hypertension. Sympatholytic and adrenolytic agents useful in the treatment of vasospastic conditions and the diagnosis of pheochromocytoma are discussed in the chapter on autonomic drugs.

**ALKAVERVIR.**—**Veriloid (RIKER).**—Alkavervir is a mixture of alkaloids obtained by the selective extraction of *Veratum viride*-N.F. with various organic solvents and selective precipitation from acidic and basic solutions.

**Physical Properties.**—Alkavervir is a light yellow powder with a

strongly sternutatory action. It is freely soluble in alcohol and acetone, but is practically insoluble in water.

**Actions and Uses.**—Alkavervir is a reproducible extract of *Vera-trum viride* assayed for the total hypotensive effect of its component alkaloids. When administered intravenously, it produces prompt lowering of the blood pressure and concomitant slowing of the heart rate in both normotensive and hypertensive animals and man. The mechanism of action is believed to be a centrally induced dilatation of arterioles accompanied by constriction of the venous vascular beds. Its action on smooth muscle of the gastro-intestinal tract is spasmogenic. Cardiac output and cerebral blood flow are not reduced, nor is renal function compromised. Its hypotensive effect reduces both systolic and diastolic tension independent of alterations in heart rate. The extract produces variable effects on the blood flow, but has not increased the number or severity of attacks in patients with angina. The chief side effects in order of appearance are substernal or epigastric burning, salivation, nausea and vomiting. These frequently can be avoided by employment of slow intravenous infusion. Extreme overdosage leads to bradycardia (readily overcome by atropine) and to hypotension and collapse (which can be counteracted by pressor amines, such as ephedrine and phenylephrine); large doses also produce respiratory depression which may progress at toxic levels to bronchiolar constriction and apnea. Cardiac arrhythmias may occur rarely and can be controlled by atropine. No drug has been found which will overcome the side effect of nausea. The extract is readily absorbed by the gastro-intestinal and usual parenteral routes. The extract apparently undergoes slow destruction by mobilization from its receptors, presumably in the brain. Tachyphylaxis and tolerance to its hypotensive action have not been observed clinically.

Alkavervir is effective when given orally or parenterally. The oral route is indicated in mild, moderate and malignant hypertension when blood pressure may be lowered gradually and when the potential benefit, in terms of decreased symptoms and increased life expectancy, outweighs the potential discomfort during the period of dose adjustment. The parenteral route is used when blood pressure must be lowered rapidly, as in the treatment of hypertensive crises for selected cases of eclampsia, pre-eclampsia, toxemia of pregnancy, acute glomerulonephritis and hypertensive encephalopathy. It should be employed with care in chronic uremia because such patients may have difficulty in adjusting to lowered blood pressure levels. It should be used with caution in patients receiving quinidine therapy. It is contraindicated in hypotension, coarctation of the aorta, pheochromocytoma (less effective than other measures), digitalis intoxication and high intracranial pressure not secondary to hypertension. Anesthetic agents do not interfere with hypotensive action of the extract, but their effect on blood pressure must be considered in determining the dose of alkavervir when it is used in conjunction with anesthesia. Drugs of the morphine series have additive but not synergistic action with the bradycardiac action of alkavervir. It also summates the heightened



cardiac irritability produced by digitalis. It is considered unwise to employ diuretics during hypotensive therapy.

**Dosage.**—Alkavervir is administered orally and parenterally. Intravenous injection provides a more prompt hypotensive effect than does intramuscular injection. Oral administration produces less intense and still slower action; hypotensive effect is reached after 2 hours but is more lasting—4 to 6 hours.

Alkavervir is administered intravenously as a solution containing 0.4 mg. of the dried extract per cubic centimeter. The dosage for the initial injection is estimated on the basis of 0.15 cc. of such solution for each 10 lb. (4.53 Kg.) of usual or estimated body weight, whichever may be lower. This amount is then diluted to 10 cc. with sterile isotonic sodium chloride solution or 5 per cent dextrose solution. The speed of injection should be at the rate of 0.5 cc. of the diluted solution per minute for a total of 4 cc. (8 minutes), and a check of the blood pressure should be made at least once every minute. After a wait of 2 minutes, the injection is continued at the same rate, again checking blood pressure until an additional 3 cc. (6 minutes) are given. Following another interval of 2 minutes, the injection is resumed at the same rate and the blood pressure is observed closely until the remaining 3 cc. of diluted solution is injected.

*The administration should be interrupted whenever either the systolic or diastolic blood pressure falls as much as 20 mm. of mercury and it should be discontinued if either gross irregularity of the pulse or emesis occurs, particularly if neither symptom was present before the injection was started.*

An interval of 2 minutes should be allowed following the initial injection to permit stabilization of blood pressure and to determine if an additional injection is needed. A blood pressure range of 150/100 is generally recommended. Usually, desired lowering of blood pressure is obtained after administration of 5 to 10 cc. If a fall in tension does not result from the first 10 cc. of diluted solution, after 5 minutes the syringe is refilled with the same dilution and the same procedure is followed for the first 20 minutes. Some patients may require a total of 15 cc. or more of diluted solution before the desired level of blood pressure is obtained. The effect of the amount required to reduce pressure to the desired level usually persists for 30 to 45 minutes and requires an interval of 1½ to 3 hours to return to the hypertensive level.

In encephalopathic patients, after the blood pressure has been reduced by the initial injection, two methods of maintaining pressure at the desired level may be followed according to the judgment of the clinician. Maintenance therapy can be provided by almost continuous slow intravenous infusion to keep the tension at the desired level for as long as this is feasible, usually several days, or by repeated slow injections like those used initially. With the latter method, the blood pressure is allowed to return to the preceding preinjection level between each injection until reflex adjustment takes place and previous hypertensive levels no longer occur. As many as six such injections have been employed in a single case. For the first method of maintenance, the dosage is based



upon 0.6 cc. of undiluted solution per 10 lb. (4.53 Kg.) of body weight. This solution is added to a liter of 5 per cent dextrose solution for injection and administered at the rate of 30 drops per minute. The usual effective dose by this method does not exceed 100 cc. of the diluted solution per hour. The infusion should be maintained at a rate which will hold blood pressure to the desired level without inducing emesis.

*It is important that a period of rapid infusion should not occur during the time when the rates of flow are being adjusted. During infusion the patient should be under constant observation and the blood pressure checked at least every 10 to 15 minutes. A solution of ephedrine sulfate 2.5 per cent (25 mg.) to combat an excessive fall in blood pressure and of atropine sulfate 1:1,000 (1 cc. ampul) to overcome bradycardia should be available at the bedside for intramuscular injection whenever this may become necessary during the administration of alkavervir.*

Alkavervir is administered intramuscularly as a solution containing 1 mg. of the dried extract per cubic centimeter. When this route is used to prolong the hypotensive action following intravenous therapy, the intramuscular dose can be translated from the body weight of the patient and the previous dose in cubic centimeters of the diluted intravenous solution of 0.4 mg. per cubic centimeter. Thus if the previous diluted intravenous dose was 5 or 6 cc., a patient weighing 140 to 165 lb. (63.5 to 74.8 Kg.) would require a dose of 0.5 cc. of the intramuscular concentration. A table for conversion of the diluted intravenous to the undiluted intramuscular dosage is available. When the intramuscular route is used for initiating therapy, the dose should be estimated on the basis of 0.25 cc. per 50 lb. (22.5 Kg.) of body weight of the solution containing 1 mg. per cubic centimeter, except that the initial dose should not exceed 1 cc. The blood pressure should be determined during the first hour at not less than 15 minute intervals. A tourniquet may be useful to slow absorption if there are early signs of overdosage. The intramuscular dose produces its maximum effect in about 60 to 90 minutes. Subsequent intramuscular doses should be administered when the blood pressure has returned to about three-fourths of the original pretreatment level. When the first dose is too small to lower the pressure, a further injection should not be administered until a lapse of 2 to 3 hours following the initial dose. The size of the second and subsequent intramuscular doses should be governed by the response of the patient to the previous injection. For adults the dose should be adjusted by 0.25 cc. increments or decrements, using proportionately smaller deviations in children.

Alkavervir is administered orally in a daily dosage of 9 to 15 mg., given in three divided doses every 6 to 8 hours. The first dose should be administered after breakfast; the evening dose may be 1 or 2 mg. larger than the other two doses of the day. Starting dosage should be smaller for patients of light weight with mild to moderate hypertension; larger starting doses may be used for overweight persons or persons with severe hypertension. Dosage must be individualized to the maximum that can be tolerated without nausea or other manifestation of excessive intake. Increases should

never exceed more than 1 mg. per dose (three times daily) nor be made oftener than every 3 to 4 days. Mild reactions (esophageal and/or substernal burning with or without sialorrhea) are valuable indicators of dosage limits and should be followed by reduction in dosage. Periodic interruptions in therapy may be necessary to prevent the tendency toward nausea. Occasionally, tolerated doses may relieve symptoms without producing a significant drop in blood pressure.

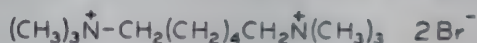
**RIKER LABORATORIES, INC.**

**Solution Veriloid (*Intravenous*):** 5 cc. ampuls. A 0.25 per cent acetic acid solution containing 0.4 mg. of alkavervir in each cubic centimeter. Packaged with or without 20 cc. ampuls of 5 per cent dextrose injection.

**Solution Veriloid with Procaine Hydrochloride 1% (*Intramuscular*):** 2 cc. ampuls. A 0.25 per cent acetic acid solution containing 1 mg. of alkavervir in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium bisulfite.

**Tablets Veriloid:** 1, 2 and 3 mg.

**HEXAMETHONIUM BROMIDE.—Bistrium Bromide (SQUIBB).—**Hexamethylenebis(trimethylammonium bromide).—The structural formula of hexamethonium bromide may be represented as follows:



**Physical Properties.**—Hexamethonium bromide is a white, tasteless, crystalline material with a faintly aromatic odor. Hexamethonium bromide is freely soluble in methanol and water, soluble in alcohol and insoluble in ether. The pH of a 1 per cent solution is 6.2 to 7.0.

**Actions and Uses.**—Hexamethonium bromide is similar in its actions and uses to the salts of other quaternary ammonium compounds, such as tetraethylammonium chloride, which act as ganglionic blocking agents. Hexamethonium inhibits the transmission of nerve impulses through both the sympathetic and parasympathetic ganglia of the autonomic nervous system. Interference with the transmission of sympathetic stimuli causing vasospasm, particularly in the lower extremities, produces increased blood flow and hypotension. Simultaneous interference with the transmission of parasympathetic impulses produces loss of ocular accommodation, cessation or decrease of motility of the gastro-intestinal tract and alteration of bladder function.

Hexamethonium bromide is of limited clinical usefulness as a therapeutic and diagnostic agent in the management of peripheral vascular diseases. It may be beneficial in the treatment of thromboangiitis obliterans, arteriosclerosis obliterans, arterial embolism, diabetic gangrene, herpes zoster, acute thrombophlebitis, Raynaud's disease, acrocyanosis, trench foot, immersion foot and various causalgias, including reflex dystrophy. It may be employed diag-



nostically in acrovascular conditions to estimate the contribution of sympathetic stimuli in the production of vasospasm.

Hexamethonium bromide is also useful in the management of selected cases of hypertension. The drug is more effective for controlling episodes of severely elevated blood pressure than for mild hypertension. It may be helpful when used with caution in patients with severe hypertension and cardiac decompensation, but it is not likely to be effective in malignant hypertension with uremia. It should be used with caution, if at all, in patients with myocardial ischemia, cerebral ischemia or encephalopathy and renal failure.

Since hexamethonium is more slowly and less completely absorbed by oral administration than by parenteral injection, the oral route is not recommended in the therapy or diagnosis of peripheral vascular disease. Because larger doses are required to produce the effects of the drug by the oral route, the use of the bromide salt in hypertension involves the regular occurrence of bromidism, so that *it should be administered only by parenteral injection*. Injections of the drug are not cumulative, but tolerance may develop in the management of severe hypertension. Upon injection, the drug produces its effects promptly, and these usually persist from 4 to 6 hours. Following injection, the drug is excreted in the urine, whereas on oral administration, a large portion passes through the intestinal tract in the stool.

Hexamethonium may produce peripheral circulatory collapse. Because of its hypotensive action, it should be employed with caution in all elderly patients and in those with arteriosclerosis. Its use is dangerous in patients who have recently lost blood because compensatory vasoconstrictor mechanisms are blocked. Side effects occasionally observed include dilatation of the pupils, blurred vision, dryness of the mouth, postural faintness, transient nausea, vomiting or drowsiness. Constipation may occur in some patients, which often can be managed by the concomitant administration of laxatives, repeated enemas or temporary discontinuance of the drug. When the constipation is serious, paralytic ileus may result. This may be overcome by the oral administration of bethanechol chloride in doses of 5 to 10 mg. twice daily. Phenylephrine hydrochloride, 2 to 4 mg. intravenously, may be used to combat profound hypotension. Small doses should be used because hexamethonium increases the sensitivity to vasopressor agents.

**Dosage.**—Hexamethonium bromide is administered by parenteral injection, intravenously, intramuscularly or subcutaneously, depending on the rapidity of response desired. To induce ganglionic block, 90 to 135 mg. (50 to 75 mg. in terms of the ion) is given parenterally as a single dose. Heavier patients may require as much as 180 mg. (100 mg. as the ion), but the maximum dose should seldom exceed 90 mg. This produces a maximum response within a few minutes, which lasts for 1 hour and subsides gradually after 4 to 6 hours.

When repeated doses are necessary, the minimum effective dose is repeated every 6 hours, after meals and at midnight. Doses of 90 mg. or more may cause profound postural hypotension and occasionally a significant reduction in supine blood pressure.



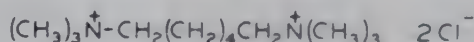
Patients receiving such doses for the first time should be kept in a recumbent position for 3 hours following the initial dose. Upon arising, each patient should be instructed to lie down at the first feeling of faintness. Subsequent doses usually do not cause such profound hypotension because of vascular adjustments. The initial dose may be given subcutaneously with the patient in a sitting position as an added precaution. For severely ill or debilitated patients, an initial dose of 1.8 to 9 mg. (1 to 5 mg. as the ion) should be used. This should be increased gradually, depending upon the response of the patient.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Solution Bistrium Bromide:** 10 cc. vials. A solution containing 44.75 mg. of hexamethonium bromide in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

U. S. trademark 562,557.

**HEXAMETHONIUM CHLORIDE.**—**Esomid Chloride** (CIBA).—**Hexameton Chloride** (BURROUGHS WELLCOME).—**Methium Chloride** (WARNER-CHILCOTT).—Hexamethylenebis(trimethylammonium chloride).—Hexamethonium chloride is commercially available in an anhydrous form and as a dihydrate. The moisture content of the dihydrate is no more than 13.3 per cent. The structural formula of hexamethonium chloride may be represented as follows:



**Physical Properties.**—Hexamethonium chloride is a white, crystalline, hygroscopic powder with a faint odor. It has a melting point between 289 and 292° (with decomposition). It is very soluble in water, soluble in alcohol, methanol and n-propanol and insoluble in chloroform and ether. The pH of a 10 per cent solution is between 5.5 and 6.5.

**Actions and Uses.**—See the monograph on hexamethonium bromide.

**Dosage.**—Hexamethonium chloride, on the basis of comparative molecular weights, provides about seven-eighths and one-third more of the cation than the same doses of the bitartrate and bromide salts, respectively. The magnitude of this difference is significant only in the comparative dose of the bitartrate, particularly when the drug is administered parenterally.

Orally, for hypotensive effect, the average total daily dosage should not exceed 3 Gm.; as much as 4 to 5 Gm. may be tolerated by some patients. For moderate to severe essential hypertension or malignant hypertension, the recommended initial dose is 0.125 Gm. four times daily (total of 0.5 Gm. each day); for patients on salt-free diets or patients who have been subjected to sympathectomy, the initial dose is 0.125 Gm. one or two times daily (total of 0.125 to 0.5 Gm. each day). These dosages may be increased gradually to tolerance. Adequate ganglionic blockade is determined by the presence of the unavoidable side effects. When this does not lower the

blood pressure to the desired level, further increases in dosage are unwarranted. Use of the drug may be continued if it relieves symptoms without further effect on the blood pressure. Reduction in the dosage to eliminate side effects results in ineffectual ganglionic blockade.

Parenterally, for peripheral vascular disease or for hypotensive effect, a solution of hexamethonium chloride may be injected in single doses of 50 to 100 mg. of the salt, and repeated every 6 hours as necessary. The maximum dose should seldom exceed 65 mg., but heavy patients may require doses up to 135 mg. For severely ill or debilitated patients, an initial trial dose of 1.3 to 6.5 mg. should be used. This may be increased gradually to tolerance.

**BURROUGHS WELLCOME & COMPANY, INC.**

**Solution Hexameton Chloride:** 10 cc. vials. A solution containing 33.8 or 135 mg. of hexamethonium chloride (25 or 100 mg. of hexamethonium ion, respectively) in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

**Tablets Hexameton Chloride:** 0.25 and 0.5 Gm.

U. S. trademark 572,762.

**CHEMO PURO MANUFACTURING CORPORATION**

**Powder Hexamethonium Chloride:** Bulk; for manufacturing use.

**CIBA PHARMACEUTICAL PRODUCTS, INC.**

**Syrup Esomid Chloride:** 473 cc. bottles. A syrup containing 62.5 mg. of hexamethonium chloride in each cubic centimeter. Preserved with 0.1 per cent sodium benzoate.

**Tablets Esomid Chloride:** 0.25 Gm.

**WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.**

**Tablets Methium Chloride:** 0.125, 0.25 and 0.5 Gm.

U. S. trademark 563,616.

**PROTOVERATRINES A AND B.—Veralba (PITMAN-MOORE).—**

Protoveratrines A and B is a mixture of two alkaloids, isolated by appropriate means from *Veratrum album*. The structural formula of the two alkaloids is not known.

**Physical Properties.**—Protoveratrines A and B is a white, odorless, slightly bitter, crystalline powder with a strongly sternutatory action, which melts between 256 and 262° (with decomposition). It is freely soluble in chloroform, very slightly soluble in ether and practically insoluble in petroleum ether and in water. Protoveratrines A and B is stable to light and air. It is stable for several months in solutions of pH 4.0 to 6.0 but is rapidly destroyed in basic and alcoholic solutions. The pH of a saturated solution is 6.5 to 7.3.

**Actions and Uses.**—Protoveratrines A and B exert their primary effect on the cardiovascular system by their influence on buffer-



reflex receptors; with therapeutic doses the mixture induces vasodilation through effects at those sites. Some investigators believe that this results in a normal physiologic redistribution of blood to all vascular beds, resulting in postural hypotension that is less severe and less frequent than with ganglionic blocking agents. Comparison of the two components of protoveratrine used in experimental animals reveals no qualitative differences in action, but protoveratrine B has about 80 per cent of the potency of protoveratrine A.

Protoveratrines A and B may be useful in the symptomatic treatment of essential hypertension, acute or chronic renal hypertension, malignant hypertension, hypertension associated with toxemia of pregnancy, and carcinoma of the adrenal cortex. Adequate dosage of the mixture produces a significant decrease in the diastolic and systolic blood pressure in most patients. This decrease is much more certain following intravenous or intramuscular injection than after oral administration. As with other *Veratrum* alkaloids, the response of different patients varies considerably and, by the oral route, the response of an individual patient occasionally varies.

Because of their powerful hypotensive effect, parenteral injection of protoveratrines A and B should be reserved chiefly for the management of hypertensive crises in which prompt lowering of the blood pressure and readily controlled dosage are essential. The oral route is suitable for the management of mild to severe hypertension in some patients. When pronounced impairment of renal function exists, adequate control of the hypertension is unlikely. Because of their hypotensive action, protoveratrines A and B may alleviate such symptoms as headache, insomnia, delirium, dizziness, blurred vision and nervousness. Their slowing effect on the heart rate may be followed by a reduction in the degree of congestive heart failure when this is caused by left ventricular failure associated with hypertension. Protoveratrines A and B also reduce hypertensive pulmonary edema and lower the elevated blood pressure occasionally encountered with cortisone therapy; they may be useful also in controlling convulsions of eclampsia.

Like other *Veratrum* alkaloids, overdosage of protoveratrines A and B produces disturbing, toxic side effects, and with therapeutic dosage, their vasodilator action is regularly accompanied by some cardiac slowing. In approximate order of appearance, side reactions include feeling of warmth or flushing, bradycardia, nausea, salivation, vomiting, cardiac arrhythmia, excessive hypotension and circulatory collapse. Occasionally a feeling of substernal pain or tightness is experienced. Unless bradycardia is severe and associated with arrhythmias, it is not necessarily harmful and may be desirable in cases of tachycardia with circulatory failure. Severe bradycardia may be overcome by an intravenous or intramuscular injection of 0.4 mg. of atropine sulfate. Parenteral injection, especially when administered too rapidly by the intravenous route, may produce sudden, excessive hypotension accompanied by collapse. This can be treated best by intramuscular injection of vasopressor



drugs, such as ephedrine (25 mg.) or phenylephrine (5 mg.). A feeling of warmth over the epigastrium, perineum, face or extremities is commonly observed, but this reaction is of minor importance and usually not unpleasant; however, gross irregularity of the pulse and nausea or vomiting appearing during intravenous administration indicate the beginning of overdosage and the need to discontinue injection. These signs (particularly nausea which is not previously present) serve as a guide to the tolerated dosage. Protoveratrines A and B should be employed cautiously in chronic uremia because such patients may have difficulty in adjusting to lowered blood pressure levels. Caution is also necessary in the presence of digitalis intoxication. Protoveratrines A and B are contraindicated in hypotension and high intracranial pressure not secondary to hypertension.

**Dosage.**—Protoveratrines A and B are administered orally, intravenously or intramuscularly. Since the effective therapeutic dose is sometimes very close to the dose which produces undesirable side reactions, it is essential to establish carefully each patient's optimum dosage schedule. Usually, this can be done best if the patient is hospitalized. The stabilized resting diastolic and systolic blood pressures should be determined prior to initiating therapy.

For the management of moderate hypertension, the usual starting oral dose for adults is 0.5 mg. after each meal and at bedtime. The blood pressure should be determined 2 to 3 hours following each dose if the patient is hospitalized. In the ambulatory patient, a daily recording of the blood pressure should be made 2 to 3 hours after the noon or evening dose. If the blood pressure is not significantly lowered, each of the four doses may be increased 0.2 mg. for the next day. Subsequent daily doses may be increased similarly until a satisfactory response is obtained. If nausea, vomiting or other side effects appear before an effective dosage level is established, the dose should be reduced by 0.1 or 0.2 mg., as may be necessary to obtain the desired effect just short of the signs of overdosage. The average effective dose varies from 0.4 to 1.5 mg. four times daily. Shorter or longer intervals may be used; or differential doses, such as a larger morning or bedtime dose with smaller interim doses, may be more effective in some patients.

Parenteral injection for the management of hypertensive crises should be initiated by the intravenous route according to one of the following methods: (1) An initial dose of 0.06 to 0.1 mg. (0.3 to 0.5 cc.) is slowly administered. If no significant decrease in blood pressure occurs, an increment of 0.02 mg. (0.1 cc.) can be repeated in 4 hours; and, if necessary, the dose can be increased by the same increment at 4-hour intervals until the desired response is obtained. As the optimal response is approached, increments of 0.01 mg. (0.05 cc.) are preferable. When toxic signs occur, one or two doses can be omitted and therapy recommenced at a lower dose. If a particularly prompt effect is necessary, the initial dose may be followed by small doses of 0.02 mg. (0.1 cc.) at 15-minute intervals. Maximum response usually appears 10 to 30 minutes after intravenous injection. Duration of action of a single intra-

venous dose extends about  $1\frac{1}{2}$  to 3 hours, but cumulative effects can result even when injections are spaced at longer intervals. (2) Slow intravenous infusion can be employed by using a more dilute solution prepared by dissolving 2 mg. of protoveratrine A and B in 200 cc. of either isotonic sodium chloride solution or 5 per cent dextrose to make a concentration of 0.001 mg. per cubic centimeter. Infusion of this dilution at the rate of 3 to 6 cc. every 10 minutes will usually decrease blood pressure significantly, and 1 to 3 cc. administered each 10 minutes is the approximate maintenance rate. (3) An alternate method of interrupted injection is the use of a 10 cc. syringe dilution of 0.1 mg. in either isotonic sodium chloride solution or 5 per cent dextrose to make a concentration of 0.01 mg. per cubic centimeter. This dilution is given at the rate of 0.5 cc. per minute for 8 minutes (total 4 cc.), during which time the blood pressure is continuously observed. After an interval of 2 minutes, the same rate is continued for 6 more minutes (3 cc.; total 7 cc.). After another 2-minute interval, the injection is continued at the same rate for an additional 6 minutes, during which time the blood pressure is checked closely (total 10 cc., which exhausts the supply in the syringe). The injection should be interrupted whenever either the systolic or diastolic pressure falls 20 mm. Hg. Three minutes is allowed for stabilization of blood pressure at the new level. If no fall results from the first 10 cc., 5 minutes should elapse; then the syringe is refilled with the same dilution, and the previous procedure is repeated. The amount required may range from 5 to 20 cc. or more, but the average effective dose is 8 to 16 cc. (0.08 mg. to 0.16 mg.).

Following the stabilization of the initial response, the effect may be maintained by slow intravenous infusion as described under (2). The patient should be under constant observation, and the blood pressure should be checked at least every 10 to 15 minutes. Care should be taken to avoid a period of rapid infusion while the rates of flow are adjusted. Some clinicians may prefer to use the dilute syringe method instead of continuous infusion to maintain the effect of the initial injection, repeating that procedure after the blood pressure has returned to a hypertensive level.

Intramuscular injection also can be used to maintain the initial response to intravenous therapy. The mixture is administered in doses of 0.16 to 0.4 mg. (0.8 to 2 cc.) every 4 to 8 hours. An alternative method is to inject an initial dose of 0.12 mg. (0.6 cc.), taking the blood pressure every 15 minutes thereafter. The maximum effect usually appears within 1 to 2 hours. If the desired response does not occur, a dose of 0.16 mg. (0.8 cc.) can be repeated after an interval of not less than 4 hours. This can be followed with 0.2 cc. increments not oftener than every 4 hours until the desired lowering of the blood pressure results. The dose established by this method usually can be repeated if the interval between injections is not less than 4 hours. Six-hour or 8-hour intervals also may be effective.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

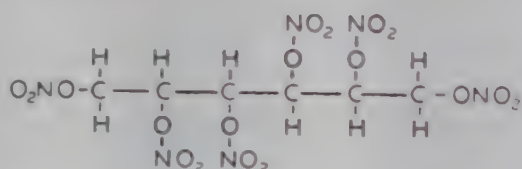
Tablets Veralba: 0.2 and 0.5 mg.



## Organic Nitrates

The esters of nitric acid and the higher alcohols (such as glycerin, propanetriol, erythrite and butanetetrol) have an action on the blood vessels similar to that of the inorganic nitrites (sodium nitrite) and that of the nitrous acid esters of the alcohols (amyl nitrite, ethyl nitrite). This is generally attributed to the fact that they form nitrites in the body.

**MANNITOL HEXANITRATE.**—An explosive compound formed by the nitration of mannitol, a sugar alcohol. The stability of the pure compound at ordinary temperatures is such that it may be used commercially but it is distinctly less stable than nitroglycerin at 75° C. It is marketed only in admixture with carbohydrate substances in dilutions of 1 part of mannitol hexanitrate to 9 or more parts of carbohydrate. In such dilutions mannitol hexanitrate is nonexplosive. The structural formula of mannitol hexanitrate may be represented as follows:



**Physical Properties.**—Mannitol hexanitrate is partially soluble in alcohol, ether and water (lactose).

**Actions and Uses.**—Mannitol hexanitrate exerts the vasodilator action of the nitrite ion ( $\text{NO}_2$ ), causing persistent relaxation of smooth muscle, especially that of the smaller blood vessels. This relaxation causes a fall in blood pressure, occurring within 15 to 30 minutes and lasting 4 to 6 hours. It also relaxes the coronary vessels in experimental animals. The action is too slow to give effective relief to attacks of angina pectoris, and, when given regularly throughout the day, it has not been proved useful in preventing attacks. The drug does not benefit most cases of essential hypertension, as it does not permanently lower blood pressure. It has no direct effect on the myocardium.

Toxic effects include the formation of methemoglobin (a warning against the use of nitrites in anemic persons), rise in intraocular tension, headache, increase in intracranial pressure and cardiovascular collapse.

**Dosage.**—Mannitol hexanitrate may be administered in 15 to 60 mg. doses at intervals of 4 to 6 hours.

THE BOWMAN BROS. DRUG COMPANY

Tablets Mannitol Hexanitrate: 32 mg.

COLE CHEMICAL COMPANY

Tablets Mannitol Hexanitrate: 32 mg.



## DIRECT LABORATORIES, INC.

Tablets Mannitol Hexanitate: 16 mg. and 32 mg.

## KEITH-VICTOR PHARMACAL COMPANY

Tablets Mannitol Hexanitate: 30 mg.

## THE NATIONAL DRUG COMPANY

Tablets Mannitol Hexanitate: 30 mg.

## PHYSICIANS' DRUG &amp; SUPPLY COMPANY

Tablets Mannitol Hexanitate: 30 mg.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Mannitol Hexanitate: 32 mg.

## RAYMER PHARMACAL COMPANY

Tablets Mannitol Hexanitate: 32 mg.

## WILLIAM H. RORER, INC.

Tablets Mannitol Hexanitate: 32 mg.

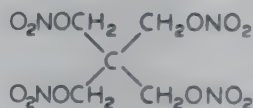
## E. R. SQUIBB &amp; SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

Tablets Mannitol Hexanitate: 16 mg. and 32.5 mg.

## S. J. TUTAG &amp; COMPANY

Tablets Mannitol Hexanitate: 32.4 mg.

**PENTAERYTHRITOL TETRANITRATE.**—Peritrate Tetranitrate (WARNER-CHILCOTT).—Pentaerythritol tetranitrate for medicinal purposes is diluted with an inert ingredient, such as lactose, since the undiluted compound may explode upon percussion. The structural formula of pentaerythritol tetranitrate may be represented as follows:



**Actions and Uses.**—Pentaerythritol tetranitrate has the same properties as other slow-acting vasodilator organic nitrate compounds, the action of which is ascribed to the release of the nitrite ion in the body. Chemically it bears a closer structural resemblance to glyceryl trinitrate (nitroglycerin) than to either erythrityl tetranitrate or mannitol hexanitate. Pentaerythritol tetranitrate releases smaller amounts of nitrite for longer periods. The drug is not intended to replace the use of glyceryl trinitrate for immediate relief of anginal attacks. Present evidence does not indicate that the drug possesses significant value in the management of hypertension. Little effect is produced on the heart rate. Moderate increase occurs in the rate and volume of respiration.

Tolerance does not appear to develop to pentaerythritol tetra-

nitrate and significant toxic manifestations have not been observed in the patients so far studied. Side effects are the same as those of other nitrates, except that these appear to be relatively infrequent and methemoglobinemia has not been demonstrated following prolonged use. Transient headache and nausea, occasionally observed, tend to disappear after 4 or 5 days of medication and have not been sufficiently severe to require discontinuing treatment. Like all nitrates, the drug should be given with caution in glaucoma, but anemia is not so far considered to be a contraindication to its use.

**Dosage.**—Pentaerythritol tetranitrate is administered orally in doses of 10 to 20 mg. three to four times daily, as may be required for maximal effect. For certain patients, adherence to a regular dosage schedule of not less than 10 mg. three or four times daily may reduce the number of anginal attacks or the severity of those attacks which are not prevented.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Pentaerythritol Tetranitrate:** Bulk; for manufacturing use. A mixture containing 75 mg. of pentaerythritol tetranitrate in each gram of powder.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

**Powder Peritrate Tetranitrate:** 30 Gm. bottles. A mixture containing 45.5 mg. of pentaerythritol tetranitrate in each gram of powder.

**Tablets Peritrate Tetranitrate:** 10 mg.

U. S. trademark 558,709.

# Central Nervous System Depressants and Stimulants

This chapter includes agents that act principally as depressants of the central nervous system and that may be used to induce sleep if pain is absent or to control convulsions. This group is to be distinguished on the one hand from the analgesics which are used to relieve pain, and on the other hand from the antispasmodics which primarily depress muscular activity. Their distinction from anesthetics is less sharp since some sedative compounds, notably the barbiturates, may be administered in doses sufficient to produce general anesthesia. Morphine and its derivatives, used mainly as analgesics, are included along with opium principles in the chapter on analgesics.

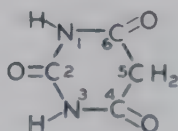
This chapter also describes drugs which stimulate the central nervous system. Picrotoxin has been included because it is particularly valuable in combating the depression of severe barbiturate intoxication.

Certain autonomic drugs that produce conspicuous central stimulating effects are considered. Aminophylline, which is useful in combating Cheyne-Stokes respiration because of its central stimulating action, is described with other theophylline and theobromine preparations in the chapter on diuretics.

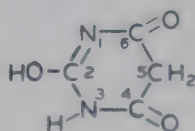
## CENTRAL NERVOUS SYSTEM DEPRESSANTS

### Barbituric Acid Derivatives

**Chemistry.**—Barbituric acid is a cyclic compound obtained by the combination of urea and malonic acid; it is also called malonyl urea. It may exist as a "keto" form (1), or as an "enol" form (2):



1



2

The latter is acidic in nature, the hydrogen atom at position 2 ionizing to produce a hydrogen ion and a barbiturate ion, and to allow the formation of metallic salts.

Barbituric acid itself does not possess hypnotic properties. These are conferred when the hydrogens on the carbon in position 5



are replaced by organic groups. Most of the clinically useful barbiturates have aliphatic radicals substituting for the hydrogen atoms; a few have alicyclic radicals. Phenobarbital is the only important barbiturate which contains an aromatic radical. Other variations in structure include the substitution of halogen for one of the hydrogens attached to the carbon in position 5, the substitution of an organic radical for the hydrogen attached to either of the nitrogens, and the replacement of oxygen attached to the carbon in position 2 with sulfur to form a thiobarbiturate.

The following compounds and their salts are official, are included in this chapter or have been described in previous editions of *New and Nonofficial Remedies*:

DURATION OF ACTION	COMPOUNDS	R <sup>1</sup>	SUBSTITUENTS R <sup>2</sup>	Other
Long	Barbital	Ethyl	Ethyl	
Long	Mephobarbital	Ethyl	Phenyl	1-Methyl
Long	Phenobarbital	Ethyl	Phenyl	
Intermediate	Amobarbital	Ethyl	Isoamyl	
Intermediate	Aprobarbital	Allyl	Isopropyl	
Intermediate	Butobarbital	Ethyl	1-Methylpropyl	
	Sodium			
Intermediate	Diallylbarbituric Acid	Allyl	Allyl	
Intermediate	Probarbital	Ethyl	Isopropyl	
	Calcium and Sodium			
Intermediate	Vinbarbital	Ethyl	1-Methyl-1-butenyl	
	Sodium			
Short	Cyclobarbital	Ethyl	Cyclohexenyl	
Short	Hexethal	Ethyl	n-Hexyl	
	Sodium			
Short	Pentobarbital	Ethyl	1-Methylbutyl	
Short	Secobarbital	Allyl	1-Methylbutyl	
Ultrashort	Hexobarbital	Methyl	Cyclohexenyl	1-Methyl
	Sodium			
Ultrashort	Thiamylal	Allyl	1-Methylbutyl	2-Thio
	Sodium			
Ultrashort	Thiopental	Ethyl	1-Methylbutyl	2-Thio
	Sodium			

Although all the barbituric acid derivatives have similar actions, they differ sufficiently so that some are effective as anti-epileptics, some as hypnotics, some as anesthetics and some as sedatives. None excels in all these categories of action.

**Duration of Action.**—The barbiturates are often classified according to the duration of their action, as long, intermediate, short and ultrashort-acting drugs. In general, the interval between the administration of the drug and the exhibition of its therapeutic effect corresponds to this classification—the short-acting drugs take effect rapidly, the long-acting drugs take effect slowly. For prolonged mild sedation in such conditions as neurasthenia and thyroid disease and to reduce the frequency of epileptic convulsions, small doses of a long-acting barbiturate are useful. The effects of the individual doses overlap and produce an evenly maintained sedation.

The long-acting barbiturates are largely excreted by the kidney; the short-acting barbiturates are destroyed to a large extent in the liver. The fate of thiopental sodium in the body has been a matter

of controversy, but evidence indicates that it, too, is destroyed in the liver. The slower the excretion or destruction of the various members of this group, the more lasting is the action. With very slow excretion, prolonged administration of ordinary doses may result in cumulative toxic effects. This is especially important when the drugs are administered to patients with damaged liver or kidneys.

**Uses.**—The derivatives of barbituric acid are effective sedatives and hypnotics, and are used in insomnia, hysteria, neurasthenia, thyroid disease, chorea, mental disturbances and epilepsy. They are used in combination with the analgesic drugs for the relief of pain, although they are not analgesic in themselves. Other specialized uses of the barbiturates include general anesthesia and basal narcosis, premedication before surgical operations, the control of pain in labor, psychiatric treatment and the prevention and treatment of convulsions. The therapeutic effects are exerted on the higher centers of the brain, and therapeutic doses do not usually cause any apparent injury to the vital organs.

Simple insomnia can be divided into two categories: one in which falling asleep is difficult, but once sleep is achieved, it is undisturbed; the other in which sleep comes easily but is disturbed by nocturnal or very early morning awakening. Drugs should not be taken routinely for either type; in fact, the use of barbiturates is much abused in insomnia. However, as temporary measures they may assist in psychotherapy, or be used to promote sleep on a particularly disturbing night. For insomnia of the first type the drug of choice is a short-acting barbiturate, which produces sleep within one-half hour and whose effect disappears within four to six hours. For the second type of insomnia, the drug of choice is an intermediate-acting barbiturate, whose effect appears later and lasts six or eight hours. The sleep induced by small doses of these drugs closely resembles natural sleep, and the patient generally awakens refreshed.

Barbiturates are valuable in the treatment of convulsions resulting from local anesthetic drugs and most other causes. The cautious intravenous administration of a short- or ultrashort-acting barbiturate is usually satisfactory in stopping a severe convulsion. For prolonged control of convulsions, as in tetanus, the drugs may be given rectally.

The barbiturates are useful in controlling excitement and manic states. Prolonged sleep induced by the barbiturates has been found useful in the treatment of psychic casualties of warfare. The intravenous barbiturates have also been found useful in the procedure of narcoanalysis. A psychiatric interview is conducted while the patient is in a semiconscious state produced by small doses of drug. Therapy of some mental disorders is rendered easier by this procedure.

The barbiturates are also used during labor, either alone or in combination with scopolamine, to produce amnesia by means of a form of twilight sleep. A frequent complication in this procedure is delirium and excitement of the mother, caused by pain which the barbiturates do not relieve. The newborn infant is also affected by



the drug given to the mother; there is an increase in the incidence of delayed respiration, and more infants than usual require resuscitation. The harmful effects upon the infant should be remembered by all who use this method, and care should be taken to avoid excessive dosage.

The barbiturates are commonly used for preanesthetic medication, either alone or in combination with other drugs. A short- or intermediate-acting drug is administered on the evening before operation to reduce apprehension and provide a restful sleep. A short-acting barbiturate is administered, often with morphine and atropine, 1 to 2 hours before operation. The barbiturates are particularly valuable for premedication when a local or regional anesthetic is to be administered, since they reduce the frequency and severity of toxic reactions to the local anesthetic drugs.

The ultrashort-acting drugs are used intravenously for induction of anesthesia and for short operations which do not require muscular relaxation. Oxygen should be given during the procedure. Mixtures of 50 per cent nitrous oxide and oxygen may be administered advantageously to improve the anesthesia and reduce the amount of barbiturate necessary. They should be administered only by those trained in anesthesia because serious or fatal complications may occur even during a minor procedure. The drugs should be administered in a 2.5 per cent solution or less, to avoid the danger of venous thrombosis. Induction is rapid and pleasant.

Respiratory depression and apnea are serious complications which may occur. The anesthetist must be capable of treating these conditions and must have equipment at hand to give artificial respiration with oxygen via a laryngeal tube. Laryngospasm and vomiting may occur. These drugs are contraindicated in shock and in operative procedures where shock may be expected. They are also contraindicated in patients with diminished pulmonary ventilation or respiratory obstruction, and in operations about the mouth and nose which may cause blood to run down the respiratory tract. Muscular relaxation with these drugs is poor, and attempts to increase the relaxation by the use of more barbiturates result in overdosage. Curare may be given to produce muscular relaxation during barbiturate anesthesia.

Basal narcosis may be produced by the rectal administration of short-acting or ultrashort-acting barbiturates. The drug is dissolved in a small volume of warm tap water and administered as a retention enema. Sleep is produced in about 10 minutes. Short minor operative procedures may be performed without further anesthesia, but for most operations the basal narcosis must be supplemented with one of the other anesthetic drugs. This method is particularly valuable for quiet induction of anesthesia in apprehensive children and in toxic thyroid patients. Thiopental sodium may be used in this manner. Prolonged convulsive states, as in tetanus, may be controlled in this manner with reduced dosage. The precautions necessary with this method are the same as those applying in intravenous barbiturate anesthesia.

**Toxicity.**—The margin between the therapeutic and toxic doses of barbiturates now in clinical use is fairly wide. Occasionally, how-

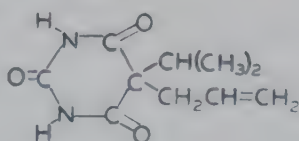


ever, even after moderate doses, lassitude, vertigo, headache, nausea and diarrhea may occur. Barbiturates are contraindicated in patients in whom they produce restlessness and excitement. Excitement and restlessness tend to occur when the barbiturates are administered to patients in severe pain. In this instance the drug does not relieve the pain but depresses the higher centers which normally act as inhibitors. Typical skin eruptions are sometimes observed, especially after prolonged administration. Long-continued use of the short-acting barbiturates may result in addiction with an abstinence syndrome which is characterized by a series of grand mal convulsions.

Poisoning with the barbiturates is a common occurrence, both by accident and with suicidal intent. The toxic effects of overdosage are respiratory depression, peripheral vascular collapse, feeble heart beat, lowered body temperature and long-continued stupor with depressed or absent reflexes. Death results from depression or paralysis of the respiration, or from pulmonary complications.

In the treatment of barbiturate poisoning the provision of adequate oxygenation is of primary importance. If there is complete respiratory paralysis, artificial respiration should be instituted at once, either manually or with a respirator or resuscitator. The use of oxygen is desirable both during artificial respiration and during the phase of depressed breathing. The cardiovascular system should be supported by intravenous infusions of saline or glucose solutions, care being taken not to overload the heart or to increase cerebral edema. Occasionally the transfusion of whole blood may be desirable. The patient should be kept warm, and his position should be changed frequently in order to prevent the onset of hypostatic pneumonia. Analeptic drugs may be administered intravenously in divided doses when there is deep coma and severe respiratory depression. These should be given until the respiration improves and the corneal reflex returns.

**APROBARBITAL.**—**Alurate** (HOFFMANN-LA ROCHE). — 5-Allyl-5-isopropylbarbituric acid. The structural formula of aprobarbital may be represented as follows:



**Physical Properties.**—Aprobarbital is a fine, white, odorless, crystalline powder with a slightly bitter taste. It melts between 140 and 141.5°. It is completely soluble in alcohol, chloroform and ether, very slightly soluble in cold water and insoluble in paraffin hydrocarbons. A saturated aqueous solution is acid to litmus.

**Actions and Uses.**—The actions and uses of aprobarbital are essentially similar to those of barbitol, but aprobarbital is more active than barbitol and is used in correspondingly smaller doses.

Fractional doses are used for sedation and larger doses for hypnosis.

**Dosage.**—For mild cases of insomnia, 65 mg. may be administered at bedtime; in obstinate cases, 0.13 Gm. may be given.

CHEMO PURO MANUFACTURING CORPORATION

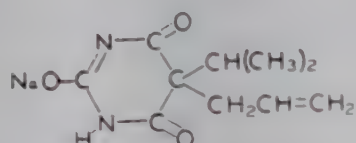
**Powder Aprobarbital:** Bulk; for manufacturing use.

HOFFMANN-LAROCHE, INC.

**Elixir Alurate:** 177.4 cc., 473 cc. and 3.78 liter bottles. A 20 per cent alcohol solution containing 8 mg. of aprobarbital in each cubic centimeter.

U. S. trademark 230,059.

**APROBARBITAL SODIUM.**—Sodium 5-allyl-5-isopropylbarbiturate. The structural formula of aprobarbital sodium may be represented as follows:



**Physical Properties.**—Aprobarbital sodium is a white, microcrystalline, hygroscopic, odorless powder with a slightly bitter taste. It is very soluble in water, very slightly soluble in alcohol and practically insoluble in ether. Aqueous solutions of aprobarbital sodium are alkaline to litmus.

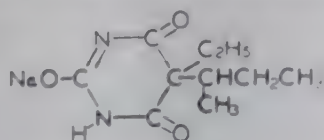
**Actions and Uses.**—See the monograph on aprobarbital. The soluble sodium salt is intended for oral or rectal administration, particularly as preanesthesia medication. Aprobarbital sodium may also be used in other cases in which large individual doses are required.

**Dosage.**—The average preoperative dose is 10 mg. per kilogram of body weight. One-third of the calculated dose is given 10 to 12 hours prior to operation (usually the evening before), the remainder, 2 hours before operation. Experience is necessary in the use of these large dosages, as they must be adjusted to the individual patient in order to avoid undesirable reactions.

CHEMO PURO MANUFACTURING CORPORATION

**Powder Aprobarbital Sodium:** Bulk; for manufacturing use.

**BUTABARBITAL SODIUM.**—Butisol Sodium (MCNEIL).—Sodium 5-*sec*-butyl-5-ethylbarbiturate. The structural formula of butabarbital sodium may be represented as follows:



**Physical Properties.**—Butabarbital sodium is a white, bitter powder. It is soluble in 6.7 parts of alcohol and in 2 parts of water and is practically insoluble in benzene and dry ether. The pH of a 1 per cent solution is between 9.0 and 10.2.

**Actions and Uses.**—Butabarbital sodium produces pharmacologic actions similar to those of other barbiturates. With average doses the rapidity and duration of its action is intermediate between the fast-acting derivative, pentobarbital, and the long-acting barbital and phenobarbital. Following oral administration the drug usually exerts initial effects within 30 minutes. Sedation is sustained for approximately 5 to 6 hours. Butabarbital sodium is thus suited to the production of a mild and more continuous depression than can be obtained with the short-acting barbiturates.

Butabarbital sodium is destroyed rapidly in the body, probably in the liver. It is excreted as such in the urine only when excessive doses are given and therefore it is not contraindicated in the presence of renal disease. Experimental studies indicate butabarbital sodium is essentially nontoxic for the liver. Its therapeutic coefficient is approximately equal to that of pentobarbital and greater than that of phenobarbital.

Butabarbital sodium is used orally as a simple sedative or hypnotic for preoperative sedation. Essentially the same clinical precautions to avoid side effects should be observed with this as with other barbiturates.

**Dosage.**—The oral sedative dose for adults ranges from 8 to 60 mg.; the oral hypnotic dose from 45 to 200 mg., depending on the purpose and the patient. The average oral adult sedative dose is 30 mg.; the average hypnotic dose, 100 mg. In general the duration of action is dependent on the size of the dose and the weight of the patient.

#### THE BOWMAN BROS. DRUG COMPANY

**Elixir Butabarbital Sodium:** 473 cc. and 3.78 liter bottles. A flavored alcohol solution containing 6.6 mg. of butabarbital sodium in each cubic centimeter.

**Tablets Butabarbital Sodium:** 16 and 32 mg.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Butabarbital Sodium:** Bulk; for manufacturing use.

#### MCNEIL LABORATORIES, INC.

**Capsules Butisol Sodium:** 0.1 Gm.

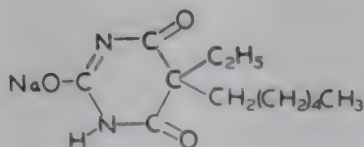
**Elixir Butisol Sodium:** A flavored alcohol solution containing 6.6 mg. of butabarbital sodium in each cubic centimeter.

**Tablets Butisol Sodium:** 15, 30, 50 and 100 mg.

U. S. trademark 378,610.

**HEXETHAL SODIUM.**—**Ortal Sodium (PARKE, DAVIS).**—Sodium 5-ethyl-5-hexylbarbiturate. The structural formula of hexethyl sodium may be represented as follows:





**Physical Properties.**—Hexethal sodium is an odorless, white or slightly yellowish powder with a bitter taste. It is very soluble in water, soluble in alcohol and practically insoluble in benzene and ether. Aqueous solutions of hexethal sodium are alkaline to litmus.

**Actions and Uses.**—The actions and uses of hexethal sodium are similar to those of barbital, but hexethal sodium is more active and is used in correspondingly smaller doses.

**Dosage.**—The usual dose is 0.2 to 0.4 Gm. followed by a glass of water. It is rarely necessary to give more than 1 Gm. in 24 hours. When oral administration is contraindicated, hexethal sodium may be administered rectally.

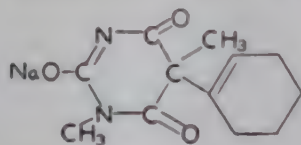
**Caution.**—*Aqueous solutions of hexethal sodium are not stable but decompose on standing; when they are boiled, precipitation occurs with evolution of ammonia.*

PARKE, DAVIS & COMPANY

Capsules Oral Sodium: 0.2 and 0.3 Gm.

U. S. trademark 302,616.

**HEXOBARBITAL SODIUM.**—Evipal Sodium (WINTHROP-STEARNs).—Sodium 5-(1-cyclohexen-1-yl)-1,5-dimethylbarbiturate. The structural formula of hexobarbital may be represented as follows:



**Physical Properties.**—Hexobarbital sodium is a white, crystalline, odorless, hygroscopic powder, with a slightly bitter taste. It is very soluble in water, freely soluble in alcohol and practically insoluble in ether. Aqueous solutions of hexobarbital sodium are alkaline to litmus. The pH of a 10 per cent solution of hexobarbital sodium is between 11 and 12.

**Actions and Uses.**—The actions and uses of hexobarbital sodium are similar to those of pentobarbital sodium except that hexobarbital sodium is designed only for intravenous use to produce anesthesia of short duration. When injected intravenously it is a quick-acting, general anesthetic. In the majority of cases consciousness is restored in 15 to 30 minutes, depending on the amount of drug injected. Drowsiness or sleep sometimes follows if the patient is left undisturbed. While the intravenous use of barbiturates is valuable under certain circumstances it should be undertaken only by those experienced in this field. Adequate facilities should be at hand to combat untoward reactions. Ataxia and transient amnesia may occasionally be encountered. Contraindica-

tions are those of the barbital compounds and general anesthetics.

**Dosage.**—As there is considerable variation in individual reactivity to any of the barbiturates, the dose must be individualized. In general, 2 to 4 cc. of a 10 per cent solution are required to induce unconsciousness in adults; this is injected intravenously at the rate of 1 cc. every 10 seconds. An additional 1 or 2 cc. may be necessary if relaxation is not obtained with the initial dose, or it may be required during the operative procedure. A total of 10 cc. of this 10 per cent solution is seldom required for adults, and it cannot be exceeded without danger.

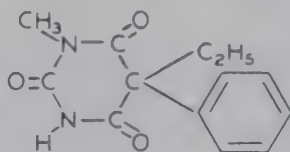
**Caution.**—*If the solution is discolored or shows the presence of undissolved particles, it should be discarded, even if it has been freshly prepared. The powder and solution undergo change on exposure to air and should not be kept for future use.*

WINTHROP-STEARNs, INC.

**Powder Evipal Sodium:** 1 Gm. ampuls.

U. S. patent 1,947,944. U. S. trademark 315,515.

**MEPHOBARBITAL.**—**Mebaral** (WINTHROP-STEARNs).—5-Ethyl-1-methyl-5-phenylbarbituric acid. The structural formula of mephobarbital may be represented as follows:



**Physical Properties.**—Mephobarbital forms white, tasteless, odorless crystals which melt between 177 and 181°. It is soluble in chloroform, slightly soluble in alcohol and ether and very slightly soluble in water. Mephobarbital dissolves in fixed alkali hydroxides and carbonates.

**Actions and Uses.**—Mephobarbital produces the sedative effect characteristic of other members of the barbiturate series. Like phenobarbital, but unlike most other members of the series, mephobarbital also exerts anticonvulsant effect by selective action on the motor cortex, presumably due to the presence of the phenyl group. Since mephobarbital has comparatively mild hypnotic action, it is better suited for use as a sedative than a soporific. Because its action in animals is not affected by the development of tolerance to other members of the barbiturate series, it is considered to have a different fate in the body than other derivatives of barbituric acid. Excretion studies in dogs indicate that at least a part of the drug may be demethylated in the body to yield phenobarbital; only traces are excreted in the urine. The extent of destruction of mephobarbital by the liver has not been determined.

Mephobarbital is chiefly employed as an anticonvulsant for the treatment of grand mal and petit mal epilepsy, though there is some difference of opinion regarding its efficacy in these conditions. It is



more effective than phenobarbital in petit mal epilepsy. It may occasionally achieve better control of both major and minor attacks of epilepsy than either phenobarbital or diphenylhydantoin sodium when given alternately or in combination with either of those drugs. Mephobarbital is inferior to phenobarbital for the management of insane epileptics, but does control seizures in epileptic psychotic persons having only moderately advanced mental changes. It does not cure congenital mental defects or the mental deterioration often observed in epileptic persons. The drug may be used in conjunction with a ketogenic diet.

Mephobarbital is also useful as a sedative, especially in the treatment of agitated, depressed and anxiety states when minimal hypnotic action is desired. Mephobarbital produces side effects of drowsiness and gait disturbance, but these are less pronounced and less persistent than similar effects of phenobarbital. Such symptoms are indications for reduction of the dosage of the drug or its temporary withdrawal. Like other barbiturates, this drug should be used with caution in patients with impaired hepatic function.

**Dosage.**—Mephobarbital is administered orally in tablets. In epilepsy, the average total daily dose for adults ranges from 0.4 to 0.6 Gm., although as little as 0.2 Gm. or as much as 0.8 Gm. may be required in some patients. Patients who have seizures principally at night and who require not more than 0.4 Gm. daily may be given the entire dose at bedtime. For attacks during the day, half the daily dose should be given during waking hours and half at night. Children under 5 years of age may be given a total daily dose of 0.03 to 0.06 Gm. and older children 0.06 to 0.3 Gm. Treatment should always be started with a small initial dose, and doses then increased gradually over a period of 4 to 5 days until the optimum dosage is determined.

In combination with phenobarbital the dose of each drug should be one-half the full dose of the drug as used alone. When the drug is employed concurrently with diphenylhydantoin sodium, the dose of the latter should be reduced, but mephobarbital may be administered in the same dosage as when it is given alone. Satisfactory results have been obtained with an average daily dose of 0.225 Gm. of diphenylhydantoin sodium plus 0.6 Gm. of mephobarbital.

As a sedative, mephobarbital may be administered in doses of 0.03 to 0.06 Gm. three or four times daily, depending on the age and condition of the patient.

CHEMO PURO MANUFACTURING CORPORATION

**Powder Mephobarbital:** Bulk; for manufacturing use.

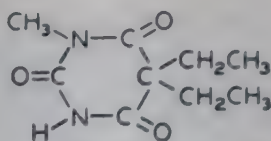
WINTHROP-STEARNES, INC.

**Tablets Mebaral:** 32, 100 and 200 mg.

U. S. patent 1,923,239. U. S. trademark 321,093.

**METHARBITAL.**—**Gemonil** (ABBOTT).—5,5-Diethyl-1-methylbarbituric acid.—The structural formula of metharbital may be represented as follows:





**Physical Properties.**—Metharbital is a white, crystalline powder with a faint aromatic odor. It has a melting point between 151 and 155°. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 4.3 Gm. in alcohol, 2.6 Gm. in ether and 0.12 Gm. in water. The pH of a saturated solution is between 5.6 and 5.7.

**Actions and Uses.**—Metharbital, a derivative of barbituric acid, shares the anticonvulsant properties of phenobarbital. The drug, therefore, is useful in the treatment of various forms of epilepsy, including grand mal, petit mal and myoclonic and mixed types of seizures. It may be effective in patients whose seizures are not controlled with other anticonvulsants, particularly in the management of myoclonic seizures and in cases attributed to organic brain damage. Conversely, it may be inferior to other agents for the management of idiopathic forms of the disease. In experimental animals the drug is effective for the control of convulsions induced by pentylenetetrazole, but less so for those induced by electroshock.

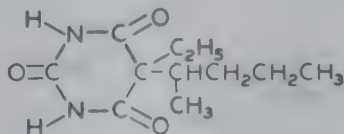
Metharbital has a low toxicity and unfavorable side effects are relatively infrequent. Drowsiness, increased irritability, rash, dizziness or stomach distress may occur. In some patients, the drug appears to be less hypnotic and depressing than phenobarbital.

**Dosage.**—Metharbital is administered orally. The initial dosage for infants and small children should be 50 mg. one to three times daily; for adults, 0.1 Gm. one to three times daily. The dosage may be increased gradually depending upon tolerance; some patients may require 0.6 to 0.8 Gm. daily to control seizures.

#### ABBOTT LABORATORIES

**Tablets Gemonil: 0.1 Gm.**

**PENTOBARBITAL.**—Nembutal (ABBOTT). — 5-Ethyl-5-(1-methyl-butyl)barbituric acid. The structural formula for pentobarbital may be represented as follows:



**Physical Properties.**—Pentobarbital is a white, granular powder. It melts between 126 and 130°. It is freely soluble in alcohol, chloroform and ether and slightly soluble in water. It dissolves in solutions of alkali hydroxides.

**Actions and Uses.**—Pentobarbital is one of the short-acting derivatives of barbituric acid. The acid has the same actions and uses as the more widely employed sodium and calcium salts.

**Dosage.**—Pentobarbital is administered in dosage equivalent to

that of pentobarbital calcium: 0.11 Gm. of pentobarbital is approximately equivalent to 0.12 Gm. of pentobarbital calcium.

Pentobarbital is marketed in the form of an elixir designed for the preoperative sedation of children: 1 to 2 years, 30 mg.; 2 to 3 years, 60 mg.; 3 to 7 years, 0.1 Gm.; 7 to 10 years, 0.12 Gm. These doses are usually administered 45 minutes before operation.

#### ABBOTT LABORATORIES

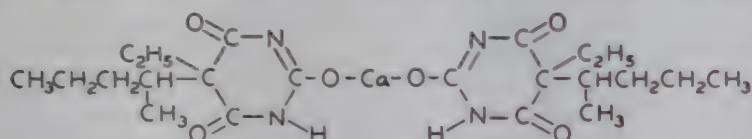
**Elixir Nembutal:** 473 cc. and 3.78 liter bottles. An 18 per cent alcohol solution containing the equivalent of 4 mg. of pentobarbital sodium in each cubic centimeter.

U. S. trademark 285,003.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Pentobarbital:** Bulk; for manufacturing use.

**PENTOBARBITAL CALCIUM.**—**Nembutal Calcium** (ABBOTT).—Calcium 5-ethyl-5-(1-methylbutyl)barbiturate. The structural formula of pentobarbital calcium may be represented as follows:



**Physical Properties.**—Pentobarbital calcium is a very fine, white powder. It is sparingly soluble in alcohol and water and practically insoluble in ether.

**Actions and Uses.**—Pentobarbital calcium shares the actions and uses of pentobarbital sodium. It has no advantage except that it is better suited for making compressed tablets and may be used when there is reason to avoid sodium. See the general statement on barbituric acid derivatives.

**Dosage.**—Pentobarbital calcium is prescribed in the same dosage as pentobarbital sodium. Orally, as a hypnotic, 0.1 Gm. is given; as a preanesthetic sedative, 0.2 Gm.

As the sodium salt, 30 mg. is administered rectally for analgesia for infants up to 1 year of age; 60 mg. for children up to 3 years of age; and 0.32 to 0.38 Gm. dissolved in a few cubic centimeters of water for adults. The average intravenous dose for adults is 0.2 to 0.3 Gm. with 0.5 Gm. as the maximum dose. The maximum dose for children has not been definitely established, although a child 6 to 12 years of age may receive up to 0.2 Gm.

#### ABBOTT LABORATORIES

**Enterab Tablets Nembutal Calcium:** 100 mg.

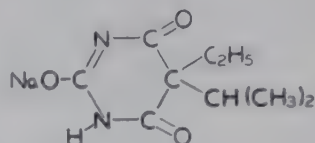
U. S. trademark 353,674 (Enterab).

**Tablets Nembutal Calcium:** 30, 50 and 100 mg.

U. S. trademark 285,003

**PROBARBITAL SODIUM.**—**Ipral Sodium** (SQUIBB).—Sodium 5-

ethyl-5-isopropylbarbiturate. The structural formula of probarbital sodium may be represented as follows:



**Physical Properties.**—Probarbital sodium is a white hygroscopic powder, soluble in water, slightly soluble in alcohol and practically insoluble in ether and chloroform. Aqueous solutions of probarbital sodium are alkaline to litmus.

**Actions and Uses.**—Probarbital sodium has the therapeutic properties of other barbituric acid derivatives. It is soluble in water and is absorbed promptly. It is excreted rapidly, but some action commonly persists for 24 hours.

Probarbital sodium is used as a hypnotic to combat restlessness, irritability and sleeplessness. Tolerance to probarbital sodium is not readily developed. It produces sleep which closely resembles the normal. The soporific effect does not wear off suddenly as with shorter-acting barbiturates.

The drug should be administered sparingly to patients in whom the proposed operation may lead to circulatory collapse and shock. For severe trauma or in the presence of shock the drug should not be administered. It is also contraindicated in patients with pulmonary disease, pulmonary edema or uncontrolled diabetes.

**Dosage.**—The sedative dose is 0.13 to 0.26 Gm.; hypnotic, 0.26 to 0.39 Gm.; preoperative, 0.52 Gm.; postoperative, 0.05 Gm.

**Caution.**—*Aqueous solutions of probarbital salts are not stable, but decompose on standing; precipitation occurs when they are boiled.*

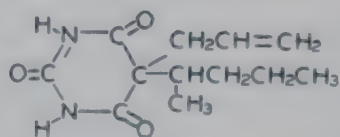
E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Elixir Ipral Sodium:** 473 cc. bottles. An elixir containing 13 mg. of probarbital sodium in each cubic centimeter.

**Tablets Ipral Sodium:** 0.26 Gm.

U. S. trademark 208,813.

**SECOBARBITAL.**—**Seconal** (LILLY).—5-Allyl-5-(1-methylbutyl) barbituric acid. The structural formula of secobarbital may be represented as follows:



**Physical Properties.**—Secobarbital is a white, amorphous, odorless powder with a slightly bitter taste, which melts at about 82°. It is very soluble in alcohol and ether, very slightly soluble in cold



water and insoluble in paraffin hydrocarbons. One gram dissolves in 8.5 ml. of 0.5 *N* sodium hydroxide. Aqueous solutions are acid to litmus.

**Actions, Uses and Dosage.**—Same as for secobarbital sodium.

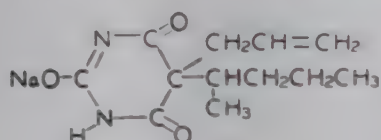
GANE'S CHEMICAL WORKS, INC.

**Powder Secobarbital:** Bulk; for compounding use.

ELI LILLY & COMPANY

**Elixir Seconal:** An elixir in a vehicle containing alcohol, glycerin, methenamine, water and aromatics, containing 4.4 mg. of secobarbital in each cubic centimeter. Methenamine increases the solubility of the barbituric acid.

**SECOBARBITAL SODIUM.**—**Seconal Sodium (LILLY).**—Sodium 5-allyl-5-(1-methylbutyl)barbiturate. The structural formula of secobarbital sodium may be represented as follows:



**Physical Properties.**—Secobarbital sodium is a white, hygroscopic, odorless powder with a bitter taste. It is very soluble in water, soluble in alcohol and practically insoluble in ether. The pH of a 5 per cent solution is between 9.8 and 10.1.

**Actions and Uses.**—The actions and uses of secobarbital sodium are essentially those of barbitol except that the former is a short-acting barbiturate. It is more active than barbitol and is used in correspondingly smaller doses.

When oral administration is contraindicated, this barbiturate may be administered rectally. Small doses are sedative; larger doses are hypnotic.

**Dosage.**—The average adult dose is 0.1 to 0.2 Gm. For use in obstetrics and for preanesthetic sedation the following dosage has been suggested: In obstetrics, an initial dose of 0.3 Gm. followed by 0.1 to 0.2 Gm. doses at appropriate intervals up to a total of no more than 1.2 Gm. within a 12-hour period; as a preanesthetic agent, 0.2 to 0.3 Gm. one-half to one hour before the patient is sent to the operating room.

AMERICAN PHARMACEUTICAL COMPANY

**Capsules Secobarbital Sodium:** 0.1 Gm.

CHEMO PURO MANUFACTURING CORPORATION

**Powder Secobarbital Sodium:** Bulk; for manufacturing use.

GANE'S CHEMICAL WORKS, INC.

**Powder Secobarbital Sodium:** Bulk; for compounding use.

## ELI LILLY &amp; COMPANY

**Powder Seconal Sodium:** 14.1 Gm. packages for compounding use.

**Powder Seconal Sodium (Sterile):** 0.25 and 0.5 Gm. ampuls. Dry powder used to prepare a 5 per cent solution by the addition of 5 cc. or 10 cc., respectively, of sterile distilled water.

**Pulvules Seconal Sodium:** 32, 50 and 100 mg.

**Suppositories Seconal Sodium:** A suppository containing 32.5, 65, 130 or 200 mg. of secobarbital sodium.

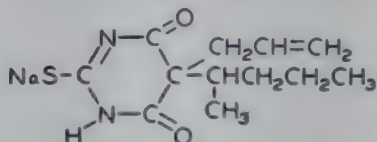
U. S. trademark 430,202.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

**Capsules Secobarbital Sodium:** 0.1 Gm.

**THIAMYLAL SODIUM.**—**Surital Sodium** (PARKE, DAVIS).—Sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate.—Thiamylal sodium is marketed as a mixture with sodium carbonate. The mixture is prepared by adding thiamylal and sodium carbonate to just enough sodium hydroxide solution to dissolve the salts. The pH is adjusted between 10.7 and 10.9. The solution is made up to volume with water and is filtered, sterilized and lyophilized.

The structural formula of thiamylal sodium may be represented as follows:



**Physical Properties.**—Thiamylal sodium (in admixture with sodium carbonate) consists of pale yellow, hygroscopic, agglutinated masses of crystals with no pronounced odor. It is freely soluble in water. The pH of a 2.5 per cent solution is about 10.8.

**Actions and Uses.**—Thiamylal sodium is an ultrashort-acting barbiturate and is particularly used for intravenous anesthesia in procedures of relatively short duration. Its anesthetic potency has been found to be about 1.4 to 1.5 times that of thiopental sodium so that smaller doses are required to produce an equivalent level of anesthesia. The cumulative effect of thiamylal sodium is reported to be less than that of thiopental sodium. Its action is rapid; anesthesia generally occurs within 20 to 60 seconds and recovery may be expected within 10 to 30 minutes after the last injection, depending upon the amount of the drug administered.

Thiamylal sodium is employed intravenously as the sole anesthetic agent in relatively short surgical procedures and as a supplement to local anesthetics during regional and spinal anesthesia or for induction prior to general anesthetics during prolonged procedures. It is compatible with the use of curare drugs employed to increase surgical relaxation. It is also administered rectally for diagnostic procedures in children.

Thiamylal sodium is detoxified by the liver and should not be

employed in patients with hepatic dysfunction or disease. It should be employed with caution in the presence of respiratory disease or obstruction, obesity, marked disturbance of arterial tension and cardiac failure or anemia. In short, this agent should be avoided whenever the intake or distribution of oxygen is impaired. It is contraindicated in traumatic shock or in conditions of impending shock.

Complications encountered are those of barbiturates in general, especially respiratory depression, hypoxia, laryngospasm, hypotension and excitement. The drug should be employed only by anesthetists familiar with the signs of anesthesia peculiar to intravenous barbiturates and the precautions in the use of these agents.

**Dosage.**—Intravenously, an initial injection of 3 to 6 cc. of a freshly prepared 2.5 per cent solution is sufficient to produce short periods of anesthesia. The rate of injection during induction should be 1 cc. every 5 seconds, and, as indicated, additional injections of 0.5 to 1 cc. are made intermittently with the needle remaining in the vein. The maximum total dose should not exceed 1 Gm. (40 cc. of a 2.5 per cent solution). As a supplement to other forms of anesthesia, the drug may be administered by continuous intravenous drip as either a 0.2 or 0.3 per cent solution. When preliminary medication has been given, induction should be delayed 30 to 45 minutes to permit this to attain its full effect.

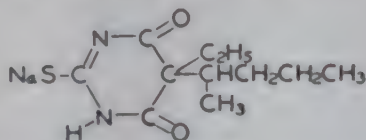
Rectally, for diagnostic procedures in children, a 5 per cent solution is used, the dosage being based upon 0.8 to 1 Gm. per 50 lb. (22.7 Kg.) of body weight.

#### PARKE, DAVIS & COMPANY

**Powder Surital Sodium:** 1 Gm. Steri-Vials packaged with or without diluent. 0.5 and 1 Gm. ampuls packaged with diluent. 5 Gm. ampuls packaged without diluent.

U. S. trademark 500,405.

**THIOPENTAL SODIUM-U.S.P.**—Pentothal Sodium (ABBOTT).—Sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate. —“Thiopental Sodium contains not less than 97 per cent of  $C_{11}H_{17}N_2NaO_2S$ , calculated on the anhydrous basis.” *U.S.P.* The structural formula of thiopental sodium may be represented as follows:



**Physical Properties.**—Thiopental sodium occurs as a yellowish white, hygroscopic powder and has a disagreeable odor. Its solutions are alkaline to litmus paper. It is soluble in water and in alcohol and insoluble in absolute ether, in benzene and in petroleum benzin. Its solution decomposes on standing; on boiling, precipitation occurs.

**Actions and Uses.**—The actions and uses of thiopental sodium are similar to those of pentobarbital sodium except that thiopental



sodium is effective in smaller doses and the action is of shorter duration. When injected intravenously it is a quick-acting, general anesthetic with early recovery occasionally marked by mental depression lasting for a few hours. Intravenous use of barbiturates may be valuable, but is potentially dangerous and should be undertaken only by experts and for short operations. Facilities must be available to handle problems involving respiratory depression, laryngospasm and carbon dioxide-oxygen balance. Atropine should be administered as premedication.

Thiopental sodium is also useful for basal anesthesia by rectal administration alone or in conjunction with other anesthetic agents. It is employed in this manner for basal anesthesia in children, in obstetrics, and for minor urologic and proctologic surgery.

The drug should not be administered to patients with respiratory embarrassment, obstruction of the respiratory passages, decompensated cardiac disease, severe anemia or hepatic cirrhosis.

**Dosage.**—2 or 3 cc. of a 2.5 per cent solution is injected intravenously in about 10 or 15 seconds. The injection is then stopped to permit the complete effect to appear in 30 to 35 seconds. If relaxation has not occurred, an additional 2 or 3 cc. may be injected at the same rate as before.

For basal anesthesia, the rectal dosage is calculated on the basis of 1 Gm. per 22.5 Kg. (50 lb.) of body weight or 0.2 cc. of a 10 per cent solution per pound of body weight. The solution is prepared by dissolving 3 Gm. in 30 cc. of water. Two-thirds of the calculated amount may be sufficient in obstetric cases. The preparation is administered rectally by syringe through a small catheter. The maximum total dose should not exceed 3 Gm. Soapsuds enemas should be avoided as soap apparently lessens the effect of the drug. The effect is maximal within about 30 minutes and lasts for about one hour. For most surgical procedures thiopental sodium must be supplemented with another anesthetic.

**Caution.**—*Aqueous solutions of thiopental sodium are not stable but decompose on standing; precipitation occurs when they are boiled.*

#### ABBOTT LABORATORIES

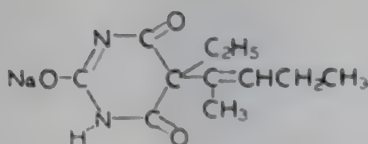
**Pentothal Sodium:** 0.5 and 1 Gm. ampuls (packaged with or without 20 and 50 cc. ampuls, respectively, of water for injection). Buffered with 30 and 60 mg., respectively, of anhydrous sodium carbonate.

5 and 10 Gm. multiple dose ampuls. Buffered with 0.3 and 0.6 Gm., respectively, of anhydrous sodium carbonate.

**Pentothal Sodium (Rectal):** 1.5 and 3 Gm. vials. Buffered with 0.09 and 0.18 Gm. of anhydrous sodium carbonate, respectively

U. S. patents 2,153,729 and 2,153,731. U. S. trademark 334,340.

**VINBARBITAL SODIUM.**—**Delvinal Sodium (SHARP & DORME).**—Sodium 5-ethyl-5(1-methyl-1-butenyl)barbiturate. The structural formula of vinbarbital sodium may be represented as follows:



**Physical Properties.**—Vinbarbital sodium is a white, odorless powder with a bitter taste. It is soluble in alcohol and water and slightly soluble in chloroform and ether. Unbuffered aqueous solutions of vinbarbital sodium are not stable. The powder is hygroscopic and if capsules containing it are broken or exposed to high humidity the contents are affected by both moisture and carbon dioxide. A 1 per cent solution has a pH between 8.5 and 9.5.

**Actions and Uses.**—The actions and uses of vinbarbital sodium are similar to those of the intermediate-acting barbituric acid derivatives. It has a short induction period and a moderate duration of action. It is used for general sedation and hypnosis, preoperative sedation, preanesthetic hypnosis, obstetrical sedation and amnesia. Its use occasionally gives rise to side effects such as epigastric discomfort, nausea, dizziness, pallor and even fall in blood pressure.

**Dosage.**—As a sedative, 30 mg. is given three to four times daily; as a sedative and hypnotic, 0.1 to 0.2 Gm.; as a preoperative hypnotic, 0.1 to 0.2 Gm.; in psychiatric cases, 0.1 to 0.4 Gm.; for obstetric sedation and amnesia, 0.2 to 0.4 Gm., with or without scopolamine. Children must be given correspondingly smaller doses.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Capsules Delvinal Sodium:** 30, 100 and 200 mg.

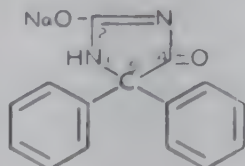
**Elixir Delvinal Sodium:** 473 cc. and 3.78 liter bottles. A 33 per cent alcohol elixir containing 8.33 mg. of vinbarbital sodium in each cubic centimeter.

**Solution Delvinal Sodium:** 5 cc. ampuls and 20 cc. vials. An aqueous propylene glycol solution containing 60 mg. of vinbarbital sodium in each cubic centimeter.

U. S. patents 2,119,526, 2,150,154, 2,187,701, 2,187,703 and 2,222,455. U. S. trademark 363,168.

## Hydantoin Derivatives

**DIPHENYLHYDANTOIN SODIUM-U.S.P.**—Dilantin Sodium (PARKE, DAVIS).—Sodium 5,5-diphenylhydantoinate.—Phenytoin sodium.—“Diphenylhydantoin Sodium, dried at 105° for 4 hours, contains not less than 98.5 per cent of  $C_{15}H_{11}N_2NaO_2$ .” U.S.P. The structural formula of diphenylhydantoin sodium may be represented as follows:





**Physical Properties.**—Diphenylhydantoin sodium is a white, odorless powder. It is somewhat hygroscopic and on exposure to air gradually absorbs carbon dioxide with the liberation of diphenylhydantoin. It is freely soluble in water, the aqueous solution usually being somewhat turbid due to partial hydrolysis. It is soluble in alcohol but practically insoluble in ether and in chloroform.

**Actions and Uses.**—Diphenylhydantoin sodium is an anticonvulsant with variable or no hypnotic action. It is more effective in controlling seizures of the grand mal type than in those of petit mal. It does not cure congenital mental defects or the mental deterioration often observed in the epileptic. Proper management of an epileptic often requires the concomitant use of several anticonvulsant drugs. Thus, phenobarbital is commonly used in conjunction with diphenylhydantoin sodium.

Side actions of varying severity include dizziness, dry skin, dermatitis, rash, itching, tremors, fever, nausea, vomiting, blurred vision, fatigue, apathy, difficult breathing and swallowing, nervousness and mental confusion with active hallucinations. Hyperplasia of the gums suggestive of scurvy may occur in young persons though its use does not interfere with the utilization of vitamin C. Diphenylhydantoin sodium is strongly alkaline and it may give rise to gastric irritation.

**Dosage.**—The optimum dosage of diphenylhydantoin sodium must be determined by the daily observation of its effects on seizures and the appearance of side actions. Mild symptoms do not necessarily require that use of the drug be stopped. The beginning adult dose is 0.1 Gm. with at least half a glass of water three times daily. If necessary this dose may be increased gradually to 0.2 Gm. three times daily. Children above the age of 6 years may be given 0.1 Gm. three times daily for one week, after which dosage may be increased if necessary to 0.1 Gm. four times daily with at least half a glass of water to prevent gastric irritation due to alkalinity. Diphenylhydantoin sodium is more rapidly effective if given before meals, but if it causes gastric irritation it should be given immediately after meals. Children under 4 years of age may start with 0.03 Gm. mixed with cream (to disguise the bitter taste and to prevent gastric irritation) twice a day. Obviously such doses require the most careful supervision. If this dose is borne without side actions the dosage may be increased to 0.03 Gm. three or four times a day. Every slight increase in dosage is made only if necessary and if no harm is to be anticipated.

The transition from phenobarbital, bromides or other hypnotic drugs to diphenylhydantoin sodium should be made gradually, with some overlapping. By this procedure the danger of phenobarbital or bromide withdrawal symptoms (increased number of seizures) is minimized, and side actions incident to the beginning of administration of diphenylhydantoin sodium are lessened.

AMERICAN PHARMACEUTICAL COMPANY, INC.

Capsules Diphenylhydantoin Sodium: 0.1 Gm.



## PARKE, DAVIS &amp; COMPANY

Kapseals Dilantin Sodium: 30 and 100 mg.

Powder Dilantin Sodium: 28.35 Gm. vials.

U. S. trademark 359,292.

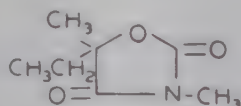
## PREMO PHARMACEUTICAL LABORATORIES, INC.

Capsules Diphenylhydantoin Sodium: 30 and 100 mg.

Powder Diphenylhydantoin Sodium: 28, 113 and 453 Gm. bottles.

## Oxazolidine Derivatives

**PARAMETHADIONE.** — **Paradione** (ABBOTT). — 3,5-Dimethyl-5-ethyloxazolidine-2,4-dione. The structural formula of paramethadione may be represented as follows:



**Physical Properties.**—Paramethadione is a clear, colorless liquid with an ester-like odor. It is freely soluble in alcohol, benzene, chloroform and ether and sparingly soluble in water. The pH of a saturated solution is about 6.4.

**Actions and Uses.**—The actions of paramethadione are similar to those of trimethadione, but the drug may be quantitatively less active. Paramethadione is indicated in the treatment of petit mal epilepsy, and other conditions for which trimethadione is used.

Paramethadione is effective in a significant number of patients not benefited by trimethadione. The reverse is also true.

The side reactions resulting from paramethadione therapy are those caused by trimethadione, except that there is less incidence of photophobia and rash. The most serious side effect, as with trimethadione, is severe leukopenia, which occurs occasionally; white blood cell counts should therefore be made bi-weekly during the first two months of therapy and at monthly intervals thereafter.

**Dosage.**—The initial dose for adults is 0.9 Gm., administered in divided doses. Thereafter, the dose should be increased or decreased to provide the smallest dose which will just control the symptoms.

For infants, the initial daily dose should be 0.3 Gm.; for children two to six years of age, 0.6 Gm. in divided doses.

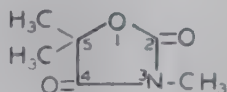
## ABBOTT LABORATORIES

Capsules Paradione: 0.15 and 0.3 Gm.

**Oral Solution Paradione:** 50 cc. dropper bottles. A 65 per cent alcohol solution containing 0.3 Gm. of paramethadione in each cubic centimeter. To be diluted before administration.

U. S. patents 2,575,693 and 2,575,692. U. S. trademark 528,247.

**TRIMETHADIONE-U.S.P.—Tridione (ABBOTT).**—3,5,5-Trimethyl-2,4-oxazolidinedione.—“Trimethadione, dried over sulfuric acid for 6 hours, contains not less than 98 per cent of  $C_6H_9NO_3$ .” *U.S.P.* The structural formula of trimethadione may be represented as follows:



**Physical Properties.**—Trimethadione is a white, granular, crystalline substance possessing a camphorlike odor. It melts at 45 to 46.5° and is soluble in water and freely soluble in alcohol and in ether. The pH of a 5 per cent solution is about 6.0.

**Actions and Uses.**—Trimethadione is primarily an antiepileptic drug and has only minor analgesic properties. It is used in the treatment of epilepsy, in which it is principally effective in cases with seizures of the true petit mal type. Its results in this condition are better in children than in adults. Trimethadione is ineffective in grand mal. It may be tried in myoclonic and akinetic seizures of organic origin but is generally less effective than in the idiopathic forms of the disease. It has been used with diphenylhydantoin sodium and/or phenobarbital in cases in which attacks are complicated by grand mal seizures. In some instances, trimethadione has increased the number of grand mal attacks as the petit mal has decreased. Combination drug therapy or readjustment of dosage may be required for optimum therapeutic effect.

Toxic reactions to trimethadione are infrequent. Gastric irritation, nausea, skin eruptions, photosensitivity and blurring of vision with a diminution in visual acuity that is reversible may be encountered and are indications for temporary withdrawal or reduction in dosage of the drug. Photophobia is less frequent in children than in adults. The skin manifestations that have been observed are not attributable to sensitization, and the visual disturbances have not been shown to be associated with optic nerve damage.

Rare cases of aplastic anemia with depression of all elements of the peripheral blood resulting from use of trimethadione indicate the need for repeated complete blood examinations of patients receiving this drug. It has been suggested that small initial doses be used and the patient cautioned to report at once any untoward symptoms that ensue. Careful medical supervision of patients under treatment with trimethadione is essential. It should not be used in the presence of anemia, leukopenia or thrombocytopenia and employed with caution if at all in blood dyscrasia.

It is contraindicated in patients with advanced renal or hepatic disease or with disease of the optic nerve.

**Dosage.**—In petit mal epilepsy, the dosage required may vary from 1 to 2 Gm. daily, given in divided doses of 0.3 Gm. three to seven times per day. In children under 6 years of age it is advisable to begin with 0.15 to 0.3 Gm. three times daily and to increase this if necessary. Optimum dosage must be determined for

each patient. Weekly, and later monthly, leukocyte counts should be made. Tablets of the drug are compounded with an appreciable amount of magnesium trisilicate as an absorbent. Large quantities of such tablets are contraindicated for children for whom a ketogenic diet has been prescribed.

#### ABBOTT LABORATORIES

**Capsules Tridione:** 0.3 Gm.

**Dulcet Tablets Tridione:** 0.15 Gm.

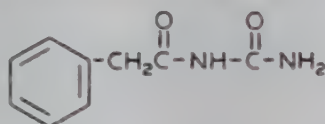
U. S. patents 2,575,692 and 2,575,694. U. S. trademark 500,527 (Dulcet).

**Solution Tridione:** 473 cc. and 3.78 liter bottles. A solution containing 40 mg. of trimethadione in each cubic centimeter.

U. S. trademark 500,401.

### Phenylacetylurea

**PHENACEMIDE.**—Phenurone (ABBOTT).—Phenylacetylurea.—The structural formula of phenacemide may be represented as follows:



**Physical Properties.**—Phenacemide is a white to creamy white, odorless, tasteless, crystalline solid. It melts between 212 and 216°. It is slightly soluble in alcohol, benzene, chloroform and ether and is very slightly soluble in water.

**Actions and Uses.**—Phenacemide is a synthetic anticonvulsant with only minor sedative action. In experimental animals the drug shows effectiveness against electroshock seizures and convulsions produced by pentylenetetrazole. Large doses produce marked ataxia and loss of reflex activity. Studies on animals also indicate that the liver plays a major role in the destruction of the drug.

Phenacemide is used in the treatment of psychomotor epilepsy, grand mal and petit mal epilepsies and in the management of mixed seizures. *The drug has serious side effects. Personality changes (including attempts at suicide and toxic psychoses), hepatic damage and bone marrow depression, as evidenced by leukopenia and aplastic anemia, have followed administration of the drug. It should be employed only by physicians experienced in the treatment of epilepsy and only in patients whose seizures are difficult or impossible to control with other recognized anticonvulsants.*

Phenacemide should not be employed in patients with evidence of liver dysfunction and should be used with caution in patients with histories of personality disorders or sensitivity to drugs. It may be advisable to hospitalize such patients for observation during the first weeks of treatment. Psychiatric signs such as withdrawal and loss of interest indicate onset of serious personality changes. Careful clinical observation throughout the course of



therapy is especially important during the first 6 months; the physician must be constantly alert for such symptoms as anorexia, nausea, vomiting, general malaise, fever, rash or jaundice, as they may be early signs of liver damage or blood dyscrasia. Anorexia, nausea and vomiting may be due to only gastro-intestinal distress, but if persistent may be of more serious significance. Patients should be instructed to report such signs immediately. Blood counts and liver function tests should be made on all patients preliminary to and regularly during treatment.

**Dosage.**—Phenacemide is administered orally and the dose determined according to the response of the patient and the degree of control already obtained with other anticonvulsant agents. It may be given in conjunction with phenobarbital, diphenylhydantoin sodium, trimethadione or paramethadione. It is recommended that when some control has been achieved with other medication, this should be continued and phenacemide added at a dosage of 0.5 Gm. three times daily with meals. The dose should be increased gradually to the minimum required for adequate control or until limiting side effects develop. The action of an average dose appears to last for 3 to 5 hours. If control by phenacemide alone is anticipated, other medication can be reduced; but if a combination of phenacemide with other drugs permits better control, or allows control with lower dosage of phenacemide or less disturbing side effects, the combination of medication should be continued. Doses as small as 0.25 Gm. three times daily may be adequate in some cases. The average total daily adult dose seldom exceeds 2 to 3 Gm. For children 5 to 10 years of age, approximately half the adult dose is recommended. The maintenance dose should be the smallest amount which will adequately control seizures. Personality disturbances, signs of liver damage, rash or depression of the blood count, particularly of erythrocytes and polymorphonuclear leukocytes, are indications for withdrawal. Cautious reinstitution of therapy may be considered when improvement occurs.

ABBOTT LABORATORIES

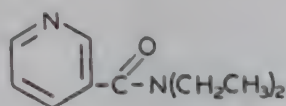
Tablets Phenurone: 0.5 Gm.

U. S. trademark 522,257.

## CENTRAL NERVOUS SYSTEM STIMULANTS

Several drugs are used occasionally as central nervous system stimulants, particularly as respiratory stimulants when the respiratory mechanism fails to respond to normal stimulation, as with carbon dioxide. The weakest and safest of these is caffeine; nikethamide is intermediate; pentyllenetetrazole (metrazol) and picrotoxin are the most potent. However, this group has few indicated uses except in the treatment of barbiturate intoxication, although the administration of oxygen, gastric lavage, artificial respiration, and maintenance of an airway may be more effective measures.

**NIKETHAMIDE-U.S.P.** — N,N-Diethylpyridine-3-carboxamide. — N,N-Diethylnicotinamide.—The structural formula of nikethamide may be represented as follows:



**Physical Properties.**—Nikethamide occurs as a clear, colorless to pale yellowish, somewhat viscous liquid, which crystallizes on standing in the cold and melts again as the temperature rises. It has a faint, characteristic, aromatic odor and a peculiar, bitter taste. Its solutions are clear and nearly colorless and have no more than a faint odor of diethylamine. It is miscible with water, with alcohol and with ether.

**Actions and Uses.**—Nikethamide acts mainly on the central nervous system. It stimulates medullary centers, increasing the rate and depth of respiration and causing peripheral vasoconstriction. Respiration is also stimulated through action on the chemoreceptors of the carotid body. In animals its administration usually results in some increase in blood pressure, but this may be preceded by a sudden temporary lowering of the pressure. Nikethamide sometimes raises blood pressure in human beings, but apparently the vasomotor center can be stimulated only under certain circumstances. Rise in blood pressure may be secondary to improved respiration and to stimulation of the reflex centers. Small doses in experimental animals exert no action on the coronary vessels, but larger doses may increase the coronary flow. However, clinical evidence for the use of nikethamide to promote increased coronary blood flow is not conclusive.

Nikethamide has been used clinically as a cardiac stimulant, but it is not especially efficient and the cardiac effect probably depends on action on respiration rather than on the myocardium. The analeptic action of nikethamide suggests its usefulness in combating acute respiratory depression from anesthetics, alcoholic intoxication and hypnotics. However, it is not clear that nikethamide is superior in this respect to other available drugs, especially in cases of barbiturate poisoning. Because of its additional action on peripheral vascular tone it is beneficial in acute circulatory failure occurring during surgical procedures or pneumonia. However, nikethamide is contraindicated in pneumonia unless circulatory collapse supervenes.

**Dosage.**—Nikethamide is available as an aqueous solution, 25 per cent W/V, for oral and for subcutaneous, intramuscular or intravenous administration, but in emergencies no benefit accrues from oral administration nor, usually, from subcutaneous administration. The drug is preferably given intravenously. Because nikethamide is rapidly inactivated after intravenous administration, the dose depends on the rate of injection. When doses larger than 3 cc. are given, the administration should be slow and the general reaction



of the patient should be watched. Large or toxic doses produce convulsions and may cause death from respiratory failure. The dose may be repeated at intervals according to the needs of the patient.

#### BUFFINGTON'S, INC.

**Solution Nikethamide 25%:** 2 and 5 cc. ampuloids. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

#### THE DRUG PRODUCTS COMPANY, INC.

**Solution Nikethamide 25%:** 1.5 cc. ampuls and 30 cc. vials. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

#### ENDO PRODUCTS, INC.

**Solution Nikethamide 25%:** 1.5 and 5 cc. ampuls and 15 cc. vials for oral administration. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

#### E. S. MILLER LABORATORIES

**Solution Nikethamide 25%:** 1.5 and 5 cc. ampuls. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

#### PREMO PHARMACEUTICAL LABORATORIES

**Solution Nikethamide 25%:** 60 and 480 cc. bottles for oral administration. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

**Solution Nikethamide 25%:** 1.5 cc. ampuls. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

#### THE UPJOHN COMPANY

**Solution Nikethamide 25%:** 1.5 and 10 cc. ampuls and 88.7 cc. bottles. A solution containing 0.25 Gm. of nikethamide in each cubic centimeter.

**PICROTOXIN-U.S.P.**—"Picrotoxin is an active principle obtained from the seed of *Anamirta Cocculus* (Linné) Wight et Arnott (Fam. *Menispermaceae*)."  
*U.S.P.*

**Physical Properties.**—Picrotoxin occurs as flexible, shining, prismatic crystals or as a micro-crystalline powder. It is odorless and stable in air but is affected by light. One gram of picrotoxin dissolves in about 350 cc. of water at 25°, in about 5 cc. of boiling water and in about 3 cc. of boiling alcohol. It is more readily soluble in diluted acids and alkalis. It is sparingly soluble in ether and in chloroform.

**Actions and Uses.**—Picrotoxin is a stimulant and convulsant which acts chiefly on the higher centers. Thus if the midbrain and pons are removed in mammals, the convulsive effect disappears, although signs of medullary stimulation may persist. The usual effects of medullary stimulation are acceleration of the respiratory rate, rise in blood pressure, slow pulse and nausea and vomiting



Picrotoxin is used principally in the treatment of severe barbiturate poisoning for its reflex activity. The drug has a special analeptic action against the narcosis induced by overdosage of barbiturates; it will overcome the depression of respiration and increase the oxygen consumption of the poisoned animal. The period of narcosis is appreciably shortened. Although highly poisonous to normal persons, the toxicity of picrotoxin appears to be less in persons narcotized by the barbiturates. The drug is rapidly destroyed in the body.

**Dosage.**—In cases of barbiturate poisoning, 6 mg. should be administered intravenously and the dose should be increased by 3 mg. increments at 15-minute intervals up to a total of 15 mg. or until the desired response is obtained. The interval between injections is important because there is a latent period between the injection and the manifestation of the full effect of the drug; failure to allow for this may lead to overdosage. Artificial respiration, an open airway, oxygen, gastric lavage and intravenous fluids should be employed concurrently with the picrotoxin therapy. An intravenous barbiturate should always be on hand to combat any incidental overdosage of picrotoxin.

#### ABBOTT LABORATORIES

**Solution Picrotoxin 0.3%:** 20 cc. vials. An isotonic sodium chloride solution containing 3 mg. of picrotoxin and 0.9 per cent benzyl alcohol in each cubic centimeter.

## Contraceptives

When protection from pregnancy is considered advisable, contraceptives are used to prevent passage of active spermatozoa from the vagina into the uterus. Whenever protection is important, occlusive devices such as diaphragms are used, reinforced by contraceptive jellies or creams. Diaphragms cannot be expected to prevent the passage around their rim of so small a body as the sperm. They make it necessary, however, for these cells, which may otherwise be deposited in immediate contact with the os, to travel 60 to 100 mm. (12,000 to 20,000 body lengths) before reaching the cervical mucus. The duration of exposure to the contraceptive material is thereby greatly increased and the effectiveness of the procedure heightened. Contraceptive jellies and creams act as chemical agents, immobilizing the spermatozoa with which they come into contact. Because of their consistency they also have an obstructive function. Accessory devices used in contraception are inserters and extractors for the diaphragms, and syringe applicators for the jellies and creams. In control of conception acceptability of the prescription probably plays a greater role in use and therefore effectiveness than in most fields of medicine. A perfume pleasing to the users, and a degree of lubrication suited to their needs may also prove important factors in contraceptive success. The esthetic block against various methods differs with the user, and variation of method by a single user often leads to greater acceptability and consequently to a higher degree of protection.

When contraceptive preparations are prescribed, the physician should warn that only by strict adherence to his directions can the maximum effect be obtained. No one method can be guaranteed 100 per cent effective although a high degree of protection can be expected if the patient has been properly examined and informed by the physician. It is difficult to make exact comparisons of the effectiveness of different contraceptive methods or materials. Errors in technic are often not recognized; semen may reach the genitalia at detumescence or removal of the condom; tears may not be noticed; and diaphragms may be placed in front of the cervix, affording no protection to the os. Most difficult to estimate are the errors of omission which occur when couples decide not to bother with the contraceptives "just this once," yet hesitate to report their responsibility for the "failure." By omitting from the computation pregnant contraceptors who admitted that they had been negligent, and by including those who were equally negligent but did not conceive, unjustifiably high estimates of protection have been secured.

Spermicidal times are used to determine the comparative effec-

tiveness of contraceptive mixtures but the circumstances of the determinations do not duplicate those of clinical use. The Brown and Gamble test employed as one of the criteria for acceptance (see the section on evaluation of certain products) requires complete mixing, which is not present clinically, and dilution to a degree which may be greater than that in the vagina. This test, however, furnishes one indication of the qualities required in contraceptives and is, perhaps, less subject to error than the test of clinical use. A description of the method and the results of its application to commercial contraceptive materials secured in 1949, was published in *J.A.M.A.* 148:50 (Jan. 5) 1952.

The status of conception control has been reviewed in a report of the Council which appeared in *J.A.M.A.* 123:1043 (Dec. 18) 1943.

For the Council's criteria for acceptance of contraceptive agents, see section on evaluation of certain products.

## APPARATUS FOR USE WITH CONTRACEPTIVES

Criteria for acceptance, and acceptance of contraceptive diaphragms and accessory devices, such as inserters and extractors, are in the purview of the Council on Physical Medicine and Rehabilitation. In *New and Nonofficial Remedies*, accepted apparatus are listed with the contraceptives with which they are used. For detailed descriptions, see "Apparatus Accepted," published by the Council on Physical Medicine and Rehabilitation.

Diaphragms listed below are usually supplied by the manufacturer in diameters differing by 5 mm. from about 55 mm. to about 100 mm.

Applicators listed below are transparent plastic syringes threaded at the blunt intravaginal end to screw onto the tubes of jelly or cream to permit filling by compression of the tube. The full capacity of the applicators (unless otherwise stated) is 5 cc., the recommended dose.

## JELLIES AND CREAMS

**Actions, Uses and Dosage.**—Jellies and creams for contraceptive use are usually introduced into the vagina on the occlusive diaphragm or cervical cap with which they are used. This agent should be introduced not more than 12 hours before sexual intercourse. A portion of the dose of jelly or cream is placed on the rim of the occlusive device, the balance on the upper side, the side which will be in contact with the cervix. A few physicians recommend the subsequent introduction of additional jelly or cream close to the occlusive device by means of a syringe applicator.

Jellies and creams may also be used without an occlusive device, but this decreases protection. Some users find this technic sufficiently more acceptable to outweigh the difference in fertility rate. When used without an occlusive device the jelly or cream is introduced into the vagina within an hour before intercourse by a syringe applicator. The recommended dose varies but is usually approximately



5 cc. To allow adequate time for the chemical to immobilize the spermatozoa, the occlusive device should not be removed nor should a douche be taken within 6 hours of ejaculation.

As most of the contraceptive diaphragms are made of rubber which will deteriorate if exposed to greases, the jellies and creams used should not contain greasy substances, such as lanolin or petrolatum.

Applicators are designed for ready filling from the container of contraceptive jelly or cream and for delivery of the recommended dose under moderate pressure into the upper vagina. Applicator should be transparent, to permit detection of air which might lead to inadequate dosage, and, if made of glass, should be sufficiently thick walled to prevent breaking in the vagina. The end should be blunt, and sufficiently large to prevent entry into the urethra.

CONTRA COMPANY, DIVISION OF SEVERNA LABORATORIES, INC.

**Contra Creme:** 63.5 Gm. collapsible tubes. A stearic acid cream having a pH of 7.3, packaged from the formula:

	Per Cent
Phenylmercuric acetate .....	0.06
Stearic acid .....	12.0
Triethanolamine .....	0.06
Glycol monostearate .....	3.5
Glycerin .....	2.5
Distilled water to make .....	100.00

U. S. trademark 355,838.

**Contra Applicator and Contra Diaphragm:** See the general statement on apparatus for use with contraceptives.

DUREX PRODUCTS, INC.

**Lactikol Creme:** 56.5 Gm., 85 Gm. and 116 Gm. collapsible tubes. A water-dispersible, nonfatty stearic acid and glyceryl monostearate cream, having a pH of 4.9, prepared from the formula:

	Per Cent
Glyceryl monoricinoleate .....	1.50
Lactic acid .....	0.50
Sodium lauryl sulfate .....	0.60
Stearic acid .....	15.00
Glyceryl monostearate .....	7.50
Glycerin .....	8.00
Perfume .....	0.07
Water sufficient to make .....	100.00

U. S. patent 2,467,884.

**Lactikol Jelly:** 62.5 Gm., 93.5 Gm. and 128 Gm. collapsible tubes. A water-soluble jelly formed from tragacanth, karaya and acacia, having a pH of 4.15, prepared from the formula:

	Per Cent
Glyceryl monoricinoleate .....	1.00
Lactic acid .....	1.50
Sodium lauryl sulfate .....	0.20
Hydroxyquinoline sulfate .....	0.05
Butyl <i>p</i> -hydroxybenzoate .....	0.02
Glycerin .....	8.00

Tragacanth .....	2.70
Karaya .....	1.00
Acacia .....	1.00
Perfume .....	0.04
Water sufficient to make .....	100.00

U. S. patent 2,467,884.

**Lactikol Metri-Dose Applicator:** Fitted at the distal end with a rubber compression bulb with central wire spring device to permit adjustment of the volume of jelly or cream to be delivered between 5 and 8 cc.

U. S. patent 2,224,018.

**Lactikol Plunger Applicator and Durex Diaphragms, Diaphragm Introducer and Fitting Rings:** See the general statement on apparatus for use with contraceptives.

#### EATON LABORATORIES, INC.

**Lorophyn Jelly:** 92 Gm. collapsible tubes. A water-soluble jelly formed from tragacanth and purified Irish moss, having a pH of 7.5, prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.05
Polyethylene glycol of monoisooctyl phenyl ether .....	0.3
Sodium borate-U.S.P. ....	3.0
Methylparaben .....	0.05
Gum tragacanth .....	1.8
Purified Irish moss .....	0.72
Glycerin .....	8.0
Water sufficient to make .....	100.00

U. S. patent 2,436,184. U. S. trademark 417,240.

**Lorophyn Jelly Applicator:** See the general statement on apparatus for use with contraceptives.

#### HOLLAND-RANTOS COMPANY, INC.

**Koromex Cream:** 78 Gm., 113 Gm. and 135 Gm. collapsible tubes. A water-soluble stearic acid emulsion having a pH of 4.2 to 4.4, prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.02
Boric acid .....	2.0
Hydroxyquinoline benzoate .....	0.02
Cetyl alcohol .....	1.0
Stearic acid .....	20.0
Butyl <i>p</i> -hydroxybenzoate .....	0.02
Sorbitan monooleate .....	5.0
Polyoxyalkalene sorbitan monostearate .....	3.0
Glycerin .....	5.0
Perfume .....	0.015
Water sufficient to make .....	100.00

U. S. trademark 213,756.

**Koromex Jelly:** 85 Gm., 128 Gm. and 142 Gm. collapsible tubes. A water-soluble jelly formed from tragacanth and gum acacia, having a pH of 4.6, prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.02
Hydroxyquinoline benzoate .....	0.02
Boric acid .....	2.0
Butyl <i>p</i> -hydroxybenzoate .....	0.02
Glycerin .....	10.0
Gum acacia .....	0.6
Tragacanth .....	2.5
Perfume .....	0.015
Water sufficient to make .....	100.00

U. S. trademark 213,756.

**Koromex Vaginal Applicator and Koromex Diaphragm:** See the general statement on apparatus for use with contraceptives.

#### LANTEEN MEDICAL LABORATORIES, INC.

**Lanteen Jelly:** 42.5 Gm., 85.35 Gm. collapsible tubes. A water-dispersible jelly having a pH of 5.2, prepared from the formula:

	Per Cent
Ricinoleic acid .....	0.50
Hexylresorcinol .....	0.10
Sodium benzoate .....	0.20
Chlorothymol .....	0.00769
Gum tragacanth .....	1.73
Starch .....	0.97
Hydrochloric acid .....	0.043
Calcium hydroxide .....	0.0264
Perfume .....	0.0126
Water sufficient to make .....	100.00

**Lanteen Applicator and Lanteen Flat Spring Mensinga Type Diaphragm:** See the general statement on apparatus for use with contraceptives.

#### LEHN & FINK PRODUCTS CORPORATION

**Lygel Vaginal Jelly:** 92 Gm. collapsible tubes. A water soluble jelly having a pH of 3.4, prepared from the formula:

	Per Cent
Benzalkonium chloride .....	0.10
Lactic acid .....	0.25
<i>p</i> -Chloro- <i>sym</i> -. <i>m</i> -xylenol .....	0.05
<i>p</i> - <i>tert</i> -.Amylphenol .....	0.05
Glycerol .....	15.00
Gum tragacanth .....	2.50
Pectin .....	1.00
Perfume oil .....	0.10
Water sufficient to make .....	100.00

U. S. trademarks 343,141 and 348,042.

**Lygel Vaginal Applicator:** See the general statement on apparatus for use with contraceptives.

U. S. patents 1,918,706; 2,077,176; 2,161,178 (applicator).

#### ORTHO PHARMACEUTICAL CORPORATION

**Ortho-Creme Vaginal Cream:** 78 and 121 Gm. collapsible tubes. A nonfatty stearic acid cream having a pH of 5.5 to 5.9, prepared from the formula:



	Per Cent
Ricinoleic acid .....	0.75
Cetyl alcohol .....	0.50
Sodium lauryl sulfate .....	0.28
Boric acid .....	2.00
Triethanolamine .....	0.25
Stearic acid .....	24.00
Glycerin .....	8.00
Perfume .....	0.05
Water sufficient to make .....	100.00

U. S. patent 2,330,846. U. S. trademark 390,141.

**Ortho-Gynol Vaginal Jelly:** 85 and 142 Gm. collapsible tubes. A water soluble jelly formed from tragacanth and acacia, having a pH of 4.5, prepared from the formula:

	Per Cent
Ricinoleic acid .....	0.70
Glacial acetic acid .....	0.33
Hydroxyquinoline sulfate .....	0.025
Boric acid .....	3.00
Diisobutylphenoxypolyethoxyethanol .....	1.00
Propylparaben .....	0.05
Glycerin .....	5.00
Acacia .....	0.53
Tragacanth .....	3.00
Perfume .....	0.025
Water sufficient to make .....	100.00

The consistency is indicated by a 50 to 55 mm. dart penetration at 40° when tested with the Braun dart penetrometer.

U. S. patents 2,330,846 and 2,541,103. U. S. trademark 298,222.

**Ortho Vaginal Applicator and Ortho Diaphragm and Ortho Diaphragm Introducer:** See the general statement on apparatus for use with contraceptives.

U. S. trademark 394,998 (applicator).

#### JULIUS SCHMID, INC.

**Ramses Vaginal Jelly:** 85 Gm. and 143 Gm. collapsible tubes. A water soluble jelly formed from carboxymethylcellulose and glycerin, having a pH of 4.5, prepared from the formula:

	Per Cent
Boric acid .....	1.00
Dodecaethylene glycol monolaurate .....	5.00
Alcohol .....	5.00
Butyl <i>p</i> -hydroxybenzoate .....	0.02
Carboxymethylcellulose sodium .....	2.50
Glycerin .....	7.00
Perfume .....	0.01
Water sufficient to make .....	100.00

U. S. patents 2,467,884 and 2,623,840. U. S. trademarks 306,696 and 401,369.

**Ramses Vaginal Applicator and Ramses Diaphragm, Diaphragm Introducer and Fitting Rings:** See the general statement on apparatus for use with contraceptives.

U. S. trademarks 284,083 (diaphragm) and 353,028 (introducer).

## TABLAX COMPANY

**Marvosan Creme:** 70.8 Gm. collapsible tubes. A stearic acid cream having a pH of 7.45, prepared from the formula:

	Per Cent
Paraformaldehyde .....	0.1
Triethanolamine .....	1.96
Methylparaben .....	0.1
Propylparaben .....	0.1
Propylene glycol .....	5.4
Glycerin .....	6.3
Sodium oleate .....	0.5
Stearic acid .....	29.8
Perfume .....	0.07
Water sufficient to make .....	100.00

U. S. trademark 278,907.

**Marvosan Applicator:** See the general statement on apparatus for use with contraceptives.

## VERITAS PRODUCTS COMPANY, INC.

**Veritas Kreme:** 70.8 and 134.6 Gm. collapsible tubes. A stearic acid cream having a pH of 7.45, prepared from the formula:

	Per Cent
Paraformaldehyde .....	0.1
Triethanolamine .....	1.96
Methylparaben .....	0.1
Propylparaben .....	0.1
Propylene glycol .....	5.4
Sodium oleate .....	0.5
Stearic acid .....	29.8
Glycerin .....	6.3
Perfume .....	0.07
Water sufficient to make .....	100.00

**Veritas Applicator and Veritas Plunger Applicator:** See the general statement on apparatus for use with contraceptives.

## WHITTAKER LABORATORIES, INC.

**Cooper Creme:** 75 Gm. collapsible tubes. A white, nongreasy, water-miscible stearate cream having a pH of 7.3 prepared from the formula:

	Per Cent
Trioxymethylene .....	0.04
Dioctyl sodium sulfosuccinate .....	0.50
Hydrous aluminum silicate .....	2.34
Trihydroxyethylamine .....	7.91
Sodium oleate .....	0.67
Stearic acid .....	23.04
Perfume (compounded oil of lavender) .....	
Water sufficient to make .....	100.00

**Cooper Creme Dosimeter** (full capacity is 10 cc.) and **Cooper Latex Diaphragm:** See the general statement on apparatus for use with contraceptives.

## CAPSULES AND SUPPOSITORIES

**Actions and Uses.**—Capsules and suppositories provide a convenient method for introducing obstructive and spermicidal material into the vagina with the advantage of freedom from the need of apparatus. The solid material introduced must be converted to a jelly or liquid form in order to cover the requisite area; hence prompt liquefaction is important. In some suppositories this results from a melting point below the temperature of the body. In others the active material is enclosed in a gelatinous shell which melts or opens when exposed to body temperature and moisture. The time required should be under 10 minutes and users should allow at least 15 minutes to elapse before intercourse. A douche should not be taken for at least 6 hours after ejaculation.

To insure further protection, physicians should advise the concurrent use of an occlusive device such as a diaphragm, and should stress the fact that suppositories or capsules used alone are less effective. If adequate time is allowed for liquefaction, the protection afforded should equal that of jelly or cream used without an occlusive device.

## EATON LABORATORIES, INC.

**Lorophyn Suppositories:** Suppositories are hermetically sealed in foil. They consist of a self-emulsifying, water-dispersible, low-melting mass prepared from the formula:

	Per Cent
Phenylmercuric acetate .....	0.05
Glyceryl monolaurate .....	10.00
Tween 61 (Sorbitan monostearatehydroxy polyoxyethyl- ene ether) .....	89.95

**Dosage.**—One suppository, containing 3 Gm.

U. S. trademark 417,240.

## LEHN &amp; FINK PRODUCTS CORPORATION

**Lygenes Vaginal Suppositories:** A vaginal suppository with an oil of theobroma base prepared from the formula:

	Per Cent
Zinc phenosulfonate .....	0.50
Hydroxyquinoline benzoate .....	0.30
<i>p</i> -Chloro- <i>sym</i> .- <i>m</i> -xyleneol .....	0.05
<i>p</i> - <i>tert</i> .-Amylphenol .....	0.05
Boric acid .....	0.10
Beeswax, white .....	5.00
Corn starch .....	9.00
Perfume .....	0.20
Cocoa butter .....	84.80

**Dosage.**—One suppository, containing 2.25 Gm.

## PRETESTED CORPORATION

**Pernox Vaginal Capsules:** A soft gelatin capsule containing a low-melting mass prepared from the formula:



	Per Cent
Ricinoleic acid .....	1.0
Dioctyl sodium sulfosuccinate .....	1.0
Propylene glycol .....	4.1
Cholesterin bodies .....	5.0
Propylene glycol monostearate .....	40.7
Anhydrous lanolin .....	24.5
Liquid petrolatum .....	17.0
Yellow petrolatum .....	2.5
Tragacanth .....	4.8

*Dosage.*—One capsule, containing 4.5 Gm.

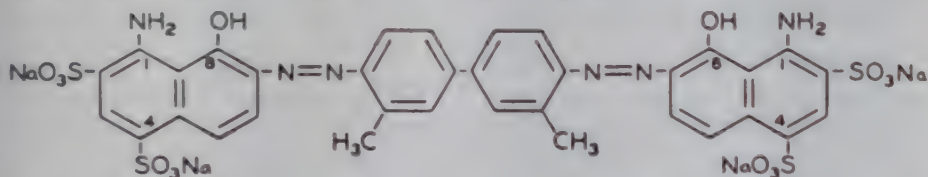
## Diagnostic Aids

In this chapter are assembled drugs that help to reveal the anatomic evidences of disease or that furnish a physiologic test of renal or hepatic function. The list includes compounds used as contrast media in roentgenography and used in testing the functional capacity of the kidneys and liver.

Allergenic extracts used for diagnosis are exempted from inclusion in N.N.R. For reference to products formerly included, see N.N.R. 1950. Toxins used in immunity tests are described in the chapter on serums and vaccines. Neostigmine and edrophonium, used in the diagnosis of myasthenia gravis, are described elsewhere—the former in the chapter on autonomic drugs, the latter in the chapter on skeletal muscle relaxants and their antagonists.

### Agents Used for Determination of Blood Volume

**EVANS BLUE.**—Tetrasodium salt of 4,4'-bis[7-(1-amino-8-hydroxy-2,4-disulfo)naphthylazo]-3,3'-bitolyl.—The structural formula of Evans blue may be represented as follows:



**Physical Properties.**—Evans blue is a bluish green or brown iridescent powder. It is very soluble in water, very slightly soluble in alcohol and practically insoluble in benzene, carbon tetrachloride and ether. The pH of a 0.5 per cent solution is between 5.5 and 7.5.

**Actions and Uses.**—Evans blue is a diazo dye that, when injected into the blood stream, combines firmly with plasma albumin and leaves the circulation very slowly. Its optical density is directly proportional to its concentration, and the maximum spectral absorption of the dye in plasma occurs where absorption of hemoglobin is so negligible that slight hemolysis does not invalidate the reading.

Evans blue is useful as an intravenous diagnostic agent for the colorimetric determination of blood volume by the plasma-dye-hematocrit method. Although the technic of the test is difficult, it gives good results when properly performed. The normal value for blood volume varies with body weight and hematocrit and cannot be stated specifically. The value for men tends to be higher than for women.

Determination of blood volume is important in the detection of impending shock. It is also important as a guide to the amount of blood, plasma or other fluids needed to avoid inadequate or excessive dosage in conditions accompanied by decreased blood volume. Such requirements are also estimated for the preoperative and postoperative management of chronically ill or debilitated patients. The use of the dye by other routes of administration or for other purposes is still in the experimental stage.

Mixing of the dye with the blood in normal persons is usually complete 9 minutes after intravenous injection; however, in patients with congestive heart disease or in severe shock, the mixing time may be prolonged to 15 minutes. The dilution of the dye in blood withdrawn serves as a quantitative indication of the volume of total circulating plasma when compared colorimetrically with the plasma of the patient before injection.

The exact final disposition of the dye in the body is not known. It is removed from the vascular system chiefly by diffusion via the capillaries into the extravascular tissues. Small amounts are excreted in the bile and also are taken up by wandering phagocytic cells. Apparently, it is not excreted in the feces and does not pass into the cerebrospinal fluid or through the placenta, and is not known to appear in the urine of patients with undamaged kidneys. Acute or chronic toxic effects have not been reported following clinical use of doses required for determination of blood volume. With doses several times greater than necessary, blue staining of the skin and sclerae occurs. Studies in animals indicate that the chief danger from high doses is the production of pulmonary emboli or lesions of the lungs. Such effects have not been observed in human beings.

**Dosage.**—Evans blue is administered intravenously with the patient in the fasting state (to avoid lipemia) and under approximate basal conditions, including recumbency for at least 15 minutes prior to the test. The dosage consists of a single injection, into the antecubital vein, of 25 mg. of dye as 5 cc. of a 0.5 per cent aqueous solution which has been further diluted with 1 to 2 cc. of isotonic sodium chloride solution. Before the dye is administered, about 10 cc. of blood is withdrawn. The tourniquet must be released promptly to avoid venous stasis which results in inaccuracy of the hematocrit value. The dye is then injected cautiously to avoid extravasation and local staining of the perivascular tissues. The syringe should be rinsed with blood several times to insure complete administration of the dye. Exactly 10 minutes after beginning the injection (15 minutes in acute shock or cardiac decompensation) a second 10 cc. sample of blood is withdrawn from the antecubital vein of the opposite arm, again with care to avoid undue stasis. Each sample is placed immediately on withdrawal into several 4 cc. hematocrit tubes containing 1 mg. of dried heparin sodium per tube to prevent coagulation. When gross hemolysis or lipemia of the plasma cannot be avoided, an extraction method should be employed. Other tests desired may be performed on the undyed sample. The hematocrit tubes are centrifuged at 3,000 rpm with a radius of 15 cm. to determine the hematocrit. Samples of



the dye-tinged and dye-free plasma are then separated from the tubes for comparison with a properly calibrated photometer. With any one manufacturer's lot of dye it is necessary to calculate the optical density of a 1:500 dilution of the dye in normal dye-free plasma when a 1 cm. cuvette is used for readings (otherwise the dilution is in proportion to the size used). The volumes of the blood components are calculated in accordance with the following formulas:

1. Total plasma vol. = [ml. of dye solution injected (5 ml.)  $\times$  dilution of standard (500)  $\times$  optical density of a standard]  $\div$  [optical density of dye-tinged plasma (unknown)]
2. Total blood vol. = Total plasma vol.  $\div$  1 - (0.96  $\times$  hematocrit)
3. Red cell vol. = Total blood vol. - Total plasma vol.

Normal values are estimated on the basis of normal body weight (in Kg.) of the patient when healthy. Experiments on men of average build indicate normal values as follows:

1. Plasma vol. in cc. = Wt. in Kg.  $\times$  45
2. Blood vol. in cc. = Wt. in Kg.  $\times$  85
3. Red cell vol. in cc. = Wt. in Kg.  $\times$  40

Values for women are usually somewhat lower.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

**Solution Evans Blue:** 5 cc. ampuls. An aqueous solution containing 5 mg. of Evans blue in each cubic centimeter. Packaged with 5 cc. ampuls of normal saline solution.

## Agents Used for Determination of Gastric Anacidity

**QUININE CARBACRYLIC RESIN.** — **Diagnex** (SQUIBB). — The quinine salt of a polyacrylic carboxylic acid resin containing about 1.85 per cent of quininium ion.

**Physical Properties.**—Quinine carbacrylic resin is a buff, odorless, tasteless, free-flowing, amorphous, granular solid. It is practically insoluble in dilute acids and alkalis, alcohol, ether and water.

**Actions and Uses.**—Quinine carbacrylic resin, a complex of quininium ion and carbacrylic resin, is employed as an indicator for the detection of gastric anacidity (achlorhydria) without intubation. After oral administration of the drug, the quinine in the resin is displaced by the hydrogen ions of free hydrochloric acid that may be present in the stomach. Approximately 1 per cent of the displaced quinine is excreted in the urine within 2 hours following administration of the resin. A stimulant to gastric secretion is given 1 hour before administration of the resin. Urine voided during that hour serves as a control sample. Assay of the quinine content of urine specimens, collected at the end of the 1-hour control period and 2 hours after administration of the

resin, is performed as an indication of the presence or absence of free hydrochloric acid in the stomach.

Assay of the urine for quinine is based on the measurement of its fluorescence in aqueous extract under ultraviolet light. Estimation of the urinary quinine level by this method may be carried out with a photoelectric fluorophotometer for direct calculation from a predetermined standard curve or by visual comparison with freshly prepared standard solutions containing known amounts of quinine. If the fluorescence of the control sample corresponds to 15 mcg. or more of quinine, the entire test should be disregarded. It indicates that the patient is excreting excessive amounts of blank fluorescent materials which may result from the use of quinine or related drugs or vitamins of the B-complex or the steroid compounds. The use of any such medication should be discontinued for 1 week and the test repeated. If the result from the control sample corresponds to 5 to 15 mcg. of quinine, the result from the test specimen should be corrected by subtracting the amount found in the control. If the amount in the control is less than 5 mcg., it may be ignored. The interpretation of the absence or presence of free gastric hydrochloric acid is as follows: Free gastric hydrochloric acid is absent if 15 mcg. of quinine or less is excreted in the 2-hour urine specimen. Free gastric hydrochloric acid is present if more than 15 mcg. of quinine is excreted in the 2-hour urine specimen. A range of quinine between 15 and 30 mcg. signifies a low degree of gastric acidity.

The quinine carbacrylic resin test does not furnish exact quantitative results; however, it is convenient for screening patients with minor gastric symptoms that are not considered sufficiently significant to warrant the discomfort of intubation gastric analysis or other more expensive diagnostic procedures. It should not be employed in lieu of more extensive examinations whenever these may be indicated. Until the physician has acquired experience with the resin method, doubtful results should be confirmed by repetition of the test after an interval of 5 to 7 days. The resin test method for achlorhydria is considered useful for the diagnosis of suspected cancer of the stomach, pernicious anemia and gastric polyps.

Quinine carbacrylic resin is of low toxicity, but it should not be given to patients with an idiosyncrasy to quinine or related drugs.

**Dosage.**—Quinine carbacrylic resin is administered orally as a single test dose of 2 Gm. in the form of granules. Patients who are given the test should be instructed not to eat after midnight preceding the day of the test. On the morning of the test, the patient should empty the bladder and discard the urine. Breakfast is withheld until the test is completed. The contents of a 0.25 Gm. capsule of caffeine and sodium benzoate is stirred and taken in one-half glass of water followed by another one-half glass of water or cup of coffee or tea, without cream, milk or sugar. One hour later or as soon thereafter as is possible, the patient voids and saves this specimen in a bottle marked "urine control." Then the 2 Gm. dose of the resin is stirred well and taken in one-fourth glass of water (without chewing the granules), followed by



another one-fourth glass of water. Exactly 2 hours after taking the resin, the urine should be voided and the entire amount saved in a bottle marked "urine sample." The bladder should be completely emptied each time; if urination ahead of the scheduled time is necessary, it should be added to that passed at the end of the designated period. After the last specimen is completed, the patient may eat breakfast. The two specimens should be delivered to a clinical laboratory as soon as it is convenient.

If desired, an injection of histamine phosphate may be used in place of oral caffeine as a stimulant to gastric secretion and the control specimen collected after a 45-minute period.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Granules Diagnex:** A quininium indicator resin, each test containing a 2 Gm. packet of quinine carbacrylic resin and a 0.25 Gm. capsule of caffeine and sodium benzoate.

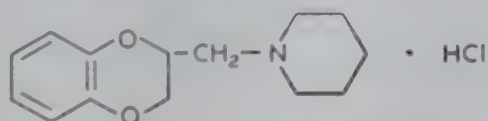
U. S. trademark 568,004.

## Agents Used in Differential Diagnosis of Hypertension

Phentolamine (Regitine) is probably even more widely used currently than piperoxan for the diagnosis of pheochromocytoma. It has little pressor action of its own. Priscoline is less often used and has no advantage over phentolamine. The "attacks" of hypertension may be brought on by administration of histamine or of tetraethylammonium chloride in minute amounts. Dibenamine has no advantage over phentolamine and is more difficult to administer. When the arterial pressure is low, agents such as histamine and tetraethylammonium chloride are the drugs of choice, but for routine screening of patients with essential or malignant hypertension, phentolamine or piperoxan are more useful.

**PHEHTOLAMINE HYDROCHLORIDE** and **PHEHTOLAMINE METHANESULFONATE**.—See the monographs in the chapter on autonomic drugs.

**PIPEROXAN HYDROCHLORIDE**. — Benodaine Hydrochloride (SHARP & DOHME).—2-(1-Piperidylmethyl)-1,4-benzodioxan hydrochloride.—The structural formula of piperoxan hydrochloride may be represented as follows:



**Physical Properties.**—Piperoxan hydrochloride is a white, crystalline, odorless powder. It melts between 232 and 236°. It is freely soluble in water, alcohol and chloroform and is very slightly soluble in benzene and ether.

**Actions and Uses.**—Piperoxan is one of a number of benzodioxan



derivatives which exert an inhibiting action on structures innervated by the sympathetic nervous system. The drug is usually designated as adrenolytic rather than sympatholytic, since it reverses the augmentor responses to epinephrine but except in very large doses does not depress peripheral sympathetic nervous system responses.

In unanesthetized animals with normal blood pressures, piperoxan may produce a slight rise, moderate fall or no effect on the blood pressure. In animals with neurogenic hypertension, piperoxan produces a temporary fall in blood pressure. Administration of piperoxan to man or animals during an infusion of epinephrine produces a fall in diastolic pressure.

It has been found clinically that patients with epinephrine-producing tumors (pheochromocytomas or paragangliomas) respond to intravenous injection of piperoxan hydrochloride with a transient fall in blood pressure. In other cases of hypertension the blood pressure is unaffected or rises slightly. The drug is thus useful in differentiating hypertension due to epinephrine-producing tumors from hypertension due to other causes.

Reported side reactions which sometimes follow intravenous administration of piperoxan hydrochloride include tachycardia, flushing, palpitation, nervousness, cold and clammy extremities, hyperpnea, mild headache, fright, sighing respiration, dizziness, substernal pressure and precordial distress. These symptoms occur almost immediately or within 1 or 2 minutes after administration, and rarely last as long as 3 minutes, although in a few instances they have lasted 20 to 25 minutes.

**Dosage.**—Piperoxan hydrochloride is administered intravenously as a diagnostic test; the recommended dose being 0.25 mg. per kilogram of body weight, up to a maximum total dose of 20 mg. No sedative should be given to the patient prior to the test. Isotonic sodium chloride solution is slowly infused into an arm vein of the supine patient. Repeated readings of blood pressure should be made until the pressure is stabilized, usually after 20 to 30 minutes. The last two readings should be made at one minute and one-half minute before administration of piperoxan hydrochloride.

The calculated dose of piperoxan hydrochloride should be administered slowly into the intravenous infusion system over a period of 2 minutes. Blood pressure readings should be made at intervals of 1 minute during the injection and for a period of 10 to 15 minutes afterward. A significant fall in blood pressure within 4 minutes (returning to normal within 15 minutes) is regarded as indicative of the presence of an epinephrine-producing tumor.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

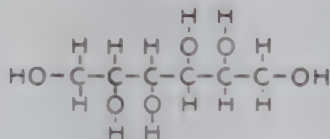
**Solution Benodaine Hydrochloride:** 10 cc. ampuls. A solution containing 2 mg. of piperoxan hydrochloride in each cubic centimeter  
U. S. patent 2,056,046. U. S. trademark 532,132.

## Agents Used for Kidney Function Tests

Glomerular filtration rate is measured by the renal plasma clearance of inulin, thiosulfate, mannitol or endogenous creatinine. Among these, inulin clearance is the most accurate measure, since mannitol is subject to approximately 10 per cent tubular reabsorption, thiosulfate apparently to some tubular excretion and reabsorption and endogenous creatinine to uncertainties as to its chemical nature and the degree of tubular excretion, particularly when the clearance rate is depressed by renal damage.

Prior to the introduction of *p*-aminohippurate, iodopyracet and iodohippurate were used for measurement of the functions of effective renal plasma flow and tubular functional capacity; iodopyracet had the wider use. These largely have been discarded in favor of *p*-aminohippurate because of the greater accuracy and facility of chemical methods for the determination of the latter compound. Iodopyracet, however, can be used advantageously for this purpose when, as during treatment with sulfonamide drugs, there is an uncertain plasma and urine *p*-amino "blank." The excretion of phenolsulfonphthalein (phenol red) is accomplished, although somewhat less effectively, by the same mechanism as the excretion of the above compounds, the presence of which will interfere with excretion of phenolsulfonphthalein. Practically, plasma clearance of phenolsulfonphthalein averages about two-thirds of effective renal plasma flow; its toxicity prevents its use for determinations of functioning tubular capacity. Probenecid blocks the tubular transfer system for these compounds in varying degree and, therefore, would interfere with interpretability of tests depending on their excretion.

**MANNITOL.**—A hexahydroxy alcohol related to mannose. The structural formula of mannitol may be represented as follows:



**Physical Properties.**—Mannitol is a white, crystalline substance with a sweet taste. It melts between 166 and 168°. It is freely soluble in water and slightly soluble in alcohol. The refractive index of a 10 per cent aqueous solution is about 1.3478.

**Actions and Uses.**—Mannitol is a hexahydric alcohol which is filtered at the glomeruli and is only minimally reabsorbed by the tubules. It is not secreted by the tubule cells or excreted by the tubules. Mannitol may be used to measure glomerular filtration. The normal values for the glomerular filtration rate are  $131 \pm 21.5$  cc. per minute for men and  $117 \pm 15.6$  cc. per minute for women. These values are corrected to a standard surface area of 1.73 square meters. In the presence of renal disease in which the glomeruli are damaged, glomerular filtration rates are lower than normal. The



validity of results of clearances with mannitol is questioned by some observers.

Mannitol is also useful in a 2.5 per cent solution of water as an irrigating fluid in transurethral resection of the prostate. Although water is ordinarily used alone for this purpose, the addition of mannitol renders it nonhemolytic, while retaining most of the physical properties of water. It is not sticky, has about the same refractive index, exerts no unfavorable effect on diabetes and produces an osmotic, diuretic action. Its use eliminates the hemolytic action of plain water, the entrance of hemolyzed blood into the circulation and the resulting hemoglobinemia which is considered a major factor in producing serious renal complications.

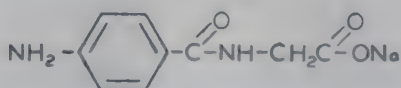
**Dosage.**—Mannitol is administered as a sterile 25 per cent solution by venoclysis. The concentration of mannitol is determined in milligrams per cubic centimeter of blood plasma. The urine formed during a definite period is collected, and the mannitol excreted is calculated in milligrams per minute. The glomerular filtration rate in cubic centimeters per minute is the number of cubic centimeters of plasma that must have been filtered at the glomerulus to supply the amount of mannitol excreted in the urine per minute.

Mannitol is also employed in a 2.5 per cent solution of water as an irrigant for transurethral resection. The irrigating solution is prepared by adding 100 cc. of a 25 per cent injectable solution to 900 cc. of distilled water.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Solution Mannitol:** 50 cc. ampuls. A sterile solution containing 0.25 Gm. of mannitol in each cubic centimeter.

**SODIUM *p*-AMINOHIPPURATE.**—Sodium *p*-aminohippurate is prepared by reacting *p*-aminohippuric acid with the theoretical amount of sodium hydroxide and adjusting the pH of the resulting solution between 7.0 and 7.2 by means of citric acid-U.S.P. The salt is not isolated from this solution. The structural formula of sodium *p*-aminohippurate may be represented as follows:



**Physical Properties.**—The pH of the ampul solution of sodium *p*-aminohippurate is not less than 7.0 nor more than 7.6.

**Actions and Uses.**—Sodium *p*-aminohippurate is filtered by the glomeruli and excreted by the tubular epithelium of the kidneys. It may be used to measure the effective renal plasma flow and to determine the functional capacity of the tubular excretory mechanism. To measure renal plasma flow, low plasma concentrations of sodium *p*-aminohippurate (1 to 2 mg. per 100 cc.) are necessary. At these concentrations 88 per cent of this compound is removed by the normal kidney from the renal blood stream in a single circulation. When the excretory capacity of the tubule cells



is impaired, renal blood flow as determined by sodium *p*-aminohippurate may be less than that determined directly. The normal effective renal plasma flow is  $697 \pm 135.9$  cc. per minute for men and  $594 \pm 102.4$  cc. per minute for women. This test cannot be applied to patients receiving sulfonamide compounds, because these develop color with the reagents used in the test.

To determine the functional capacity of the tubular excretory mechanism high plasma concentrations (40 to 60 mg. per 100 cc.) of sodium *p*-aminohippurate must be used. The normal mean value of the "tubular excretory mass" is  $77.5 \pm 12.9$  mg. per minute.

**Dosage.**—To determine effective renal plasma flow, a sterile solution of sodium *p*-aminohippurate is injected intravenously in a volume sufficient to produce approximately 2 mg. of *p*-aminohippurate per 100 cc. of blood plasma. At this plasma level all the *p*-aminohippurate in the blood that passes through the normal kidney is removed and appears in the urine. The urine formed during a definite but short period is collected, and the average amount of *p*-aminohippurate eliminated is calculated in milligrams per minute. This value divided by the *p*-aminohippurate content of the plasma in milligrams per cubic centimeter is equivalent to the number of cubic centimeters of plasma per minute that must have passed through the kidneys (effective renal plasma flow).

To determine tubular excretory mass, a sterile solution of sodium *p*-aminohippurate is injected intravenously in a volume sufficient to "saturate" the capacity of the tubular cells to excrete *p*-aminohippurate (40 to 60 mg. per 100 cc. of plasma), and the *p*-aminohippurate content of the plasma is determined in milligrams per cubic centimeter. The amount excreted in the urine is determined in milligrams per minute, this value including both glomerular filtration and tubular excretion. The glomerular filtration rate, using mannitol, a compound that is filtered only through the glomeruli, is determined in cubic centimeters per minute (see the monograph on mannitol). From the glomerular filtration rate and the *p*-aminohippurate content per cubic centimeter of plasma is calculated the amount of *p*-aminohippurate that was filtered through the glomeruli in 1 minute (cc. min.  $\times$  mg. cc.). Then the total number of milligrams excreted in the urine per minute minus the amount filtered through the glomeruli per minute equals the amount of *p*-aminohippurate in milligrams per minute excreted by the tubules (tubular excretory mass).

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Solution Sodium *p*-Aminohippurate:** 50 cc. ampuls. Each 50 cc. contains 10 Gm. of sodium *p*-aminohippurate, adjusted to a pH of 7.0 to 7.6 with sodium hydroxide.

**PHENOLSULFONPHTHALEIN.**—See the section on phenolphthalein dyes.

### Curare Preparations

See the chapter on skeletal muscle relaxants and their antagonists.

## Water-Insoluble Organic Iodine Compounds for Roentgenography

Water-insoluble organic iodine compounds are injected as contrast mediums in roentgen diagnosis, especially of tumors of the spinal cord, in the localization of bronchial and pulmonary lesions and in gynecology. Various vegetable oils may be used; animal oils cause local irritation. According to the method of iodination, the oil may contain iodine alone, or iodine and chlorine ("chloriodized oils"). These methods do not differ essentially.

Water-insoluble organic iodine compounds are quite viscid. For injections into cavities they may be rendered less viscid by the addition of ethyl oleate; they may be rendered water miscible by emulsification.

**Caution.**—"It should be emphasized that the injection of iodized oils is essentially a surgical procedure, introducing a foreign and possibly irritant body, and involving more or less risk, which should be weighed against the presumptive advantages, in comparison with the relative advantages and disadvantages of other measures. The following cautions should be especially borne in mind:

"1. Oils that have aged and darkened beyond their original color should never be used.

"2. Subarachnoid injections should be avoided, at least until all other means of diagnosis have been exhausted.

"3. Intratracheal and intrapleural injections should be avoided in tuberculosis of the respiratory organs and also when restriction of respiratory area would be contraindicated.

"4. The injection pressure should be carefully controlled, so as not to lacerate the tissues.

"5. Intra-uterine injections should be made only under fluoroscopic observations.

"6. Iodized oil should not be used for renal pyelography, except in the form of emulsion; and the injection should be stopped if pain is felt.

"7. Intravascular injections with iodized oil appear too dangerous; the use of emulsions for this purpose requires further study." (Dangers of the Injection of Iodized Oils, Report of the Council on Pharmacy and Chemistry, J.A.M.A. 99:1946 [Dec. 3] 1932. The full report may be consulted for further discussion of the history, scope, and limitations of iodized oils.)

When the so-called per nasal method of injecting the oil into the larynx is employed, the risk of intoxication from the local anesthetic required for this procedure is greatly enhanced as the absorptive surface is increased.

**CHLORIODIZED OIL.**—*Iodochlorol* (SEARLE).—Chlorinated and iodized peanut oil. A product formed by the chemical addition of iodine monochloride to peanut oil. It contains 26.5 to 28.5 per cent of iodine in organic combination.

**Physical Properties.**—Chloriodized oil is a pale yellow, viscous,



oily liquid with a faint, bland taste. It is practically insoluble in water, slightly soluble in alcohol and freely soluble in benzene, chloroform and ether.

**Actions and Uses.**—See the general statement on water-insoluble organic iodine compounds for roentgenography.

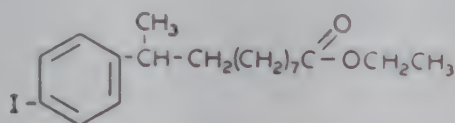
**Dosage.**—The dose varies with the capacity of the structure to be examined. It ranges from 1 or 2 cc. for small sinuses and fistulas to 20 cc. in the paranasal sinuses and bronchial tract.

G. D. SEARLE & Co.

**Iodochlorol:** 20 cc. bottles. A halogenated (chloriodized) peanut oil containing about 27 per cent iodine and 7.5 per cent chlorine in organic combination.

U. S. trademark 519,701.

**ETHYL IODOPHENYLUNDECYLATE.**—**Pantopaque (LAFAYETTE).**—A mixture of the  $\kappa$  and  $\omega$  isomers of ethyl iodophenylundecylate, which is of quite uniform, but unknown, proportions. The principal isomer is thought to be the  $\kappa$ , whose structural formula may be represented as follows:



**Physical Properties.**—Ethyl iodophenylundecylate is a colorless to pale yellow, odorless, viscous liquid. The color darkens on long exposure to air. It is freely soluble in alcohol, benzene, chloroform and ether and very slightly soluble in water.

**Actions and Uses.**—Ethyl iodophenylundecylate is an absorbable iodized fatty acid compound of low viscosity designed especially for myelography. It is particularly useful for study of the lumbar region. Intraperitoneal or oral administration in lower animals is moderately toxic, but no toxic phenomena have been observed with massive doses injected intrathecally in higher animals. It is absorbed from the peritoneal cavity of experimental animals in about 6 weeks and from the subarachnoid space of dogs in about 15 months. In humans, intrathecal injection of 2 to 5 cc. is well tolerated even when the agent is left in the spinal canal. When the bulk of the injected material is removed, the remainder is usually absorbed within 2 months. When none is removed, absorption proceeds at a variable rate depending on conditions within the spinal canal, sometimes requiring several years.

The incidence and severity of side effects following myelography with aspiration of ethyl iodophenylundecylate is only slightly greater than with ordinary lumbar puncture. In 10 to 30 per cent of patients there may be backache and transient elevation in temperature. The agent should not be employed when lumbar puncture is contraindicated, and to avoid subdural and extra-arachnoid extravasation it should not be used within 10 days of a previous lumbar puncture.



Ethyl iodophenylundecylate is also employed in emulsified aqueous form as a medium for roentgenographic visualization of the biliary tree, sinus and fistulous tracts, ducts and certain body cavities. The emulsion has some advantage over radiopaque oils because of its ability to adhere to mucous membranes, its low viscosity and surface tension and its miscibility with tissue fluids. Since it has not been found satisfactory for bronchography, it is not recommended for that purpose. For cholangiography, it is injected either through a T-tube placed in the common bile duct following surgery or through a catheter inserted into the cystic duct to permit visualization at the time of operation. For visualization of sinuses, fistulas, ducts or cavities, injection is made through a syringe needle or catheter of appropriate size, depending upon the structure to be examined. It is not necessary to remove the emulsion by aspiration or flushing except in enlarged cavities. Retention of the emulsion in enlarged cavities may interfere with subsequent examinations. The emulsion should not be used intravenously.

**Dosage.**—For myelography, ethyl iodophenylundecylate, in undiluted form, is injected intrathecally by lumbar puncture technic; the 2 to 5 cc. dose is usually injected between the third and fourth lumbar segments. Care should be exercised to ascertain that the needle point is in the subarachnoid space. The injection should be made slowly to detect unusual resistance from obstruction. The needle with adapter is left in place during myelography to implement removal of the agent when the examination is completed. The agent is removed by aspiration in conjunction with fluoroscopic visualization.

For peroperative and postoperative cholangiography or for visualization of sinus tracts, fistulas, ducts and cavities, a 50 per cent emulsion of ethyl iodophenylundecylate is injected. In cholangiography, the amount to be injected is regulated by fluoroscopic control. The injection should be made gently, and care should be taken to avoid the introduction of air bubbles. For visualization of sinuses, fistulas, ducts and body cavities, initial flushing with isotonic sodium chloride solution may be required to remove clots, mucus and foreign material prior to injection of the emulsion. It is not necessary to completely fill large cavities, but rotation of the patient may be necessary to reach all surfaces of the structure.

#### LAFAYETTE PHARMACAL INC.

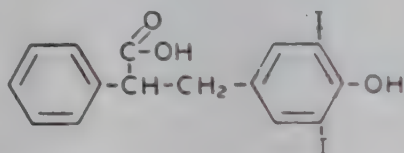
**Pantopaque:** 3 cc. ampuls. An undiluted liquid, ethyl iodophenylundecylate, containing 30.5 per cent iodine in organic combination.

**Emulsion Pantopaque 50% V/V:** 10 cc. ampuls. An emulsion containing 0.5 cc. of ethyl iodophenylundecylate in each cubic centimeter.

U. S. patent 2,348,231. U. S. trademark 401,476.

IDOALPHIONIC ACID-U.S.P. — Priodax (SCHERING). —  $\beta$ -(4-

Hydroxy-3,5-diiodophenyl)- $\alpha$ -phenylpropionic acid. — "Iodoalphonic Acid, dried over sulfuric acid for 4 hours, contains not less than 98 per cent and not more than 102 per cent of  $C_{15}H_{12}I_2O_3$ ." *U.S.P.* The structural formula of iodoalphonic acid may be represented as follows:



**Physical Properties.**—Iodoalphonic acid occurs as white crystals or as a white or faintly yellowish powder, having a faint, characteristic odor and taste. It is stable in air but is slightly discolored on prolonged exposure to light. Insoluble in water, it is readily soluble in alcohol and ether and slightly soluble in benzene and chloroform. It is soluble in both alkali carbonate and hydroxide solutions.

**Actions and Uses.**—Iodoalphonic acid is used as a medium for cholecystography. It causes less nausea, vomiting and diarrhea than tetraiodophenolphthalein. The drug is excreted primarily through the kidneys. See also the general statement on water-insoluble organic iodine compounds for roentgenography.

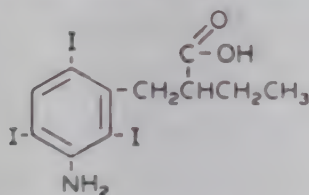
**Dosage.**—The average adult dose is 3 Gm., although more may be given. The drug should be taken with several glasses of water during or after a light fat-free meal in the late afternoon. Nothing should then be eaten until the roentgenologic examination is completed the next morning.

SCHERING CORPORATION

Tablets Priodax: 0.5 Gm.

U. S. patent 2,345,384. U. S. trademark 393,227.

IODOPANOIC ACID.—Telepaque (WINTHROP-STEARNES).— $\beta$ -(3-Amino-2,4,6-triiodophenyl)- $\alpha$ -ethylpropionic acid.—The structural formula of iodopanoic acid may be represented as follows:



**Physical Properties.**—Iodopanoic acid is a cream-colored, tasteless powder with a faintly aromatic odor. It melts between 152 and 158° and darkens on exposure to light. It is soluble in acetone, alcohol and dilute alkalis and insoluble in water.

**Actions and Uses.**—Iodopanoic acid is a water-insoluble organic iodine compound administered orally as a radiopaque medium in cholecystography. Following ingestion it is promptly absorbed, eliminated in the bile and subsequently stored in the gallbladder.



It produces dense shadows of the gallbladder usually with a single average dose, which often permits visualization of the extrahepatic ducts.

Iodopanoic acid seldom produces undesirable reactions and has a low toxicity. Occasionally, nausea and diarrhea and, rarely, dysuria have followed its administration. It is contraindicated in acute nephritis and uremia and should not be administered when disorders of the gastro-intestinal tract prevent absorption of the compound.

**Dosage.**—The usual dose is 3 Gm. administered orally 10 hours prior to the time scheduled for roentgenography. In addition, the patient should be given a fat-free meal the evening before medication and allowed nothing by mouth until roentgenograms have been taken. The patient should also be given a saline or sodium bicarbonate enema shortly before roentgenography to remove any accumulated gas; immediately following roentgenography, a high-fat meal is given. Additional films are obtained 1 to 3 hours later to determine the contractile function of the gallbladder. Visualization of the extrahepatic ducts can usually be obtained if roentgenograms are taken 10 minutes after the high-fat meal. When these structures are of particular interest, the dose of iodopanoic acid may be increased to 5 or 6 Gm.

WINTHROP-STEARNES, INC.

**Tablets Telepaque: 0.5 Gm.**

U. S. trademark 610,113.

### **Water-Soluble Organic Iodine Compounds for Roentgenography**

Satisfactory roentgenograms of the urinary tract may be secured by the intravenous injection of nontoxic soluble iodine compounds which are rapidly excreted in the urine. Several organic compounds are now available for this purpose and for ureteral retrograde pyelography. Sodium iodide, in the necessary dose, is too toxic for intravenous injection.

For intravenous urography, no fluids should be given to the patient for several hours (usually from midnight) prior to examination. Restriction of fluids permits greater concentration of the drug. The gastro-intestinal tract should be cleared of gas and retained materials by enemas and laxatives, preferably with castor oil. If the history of allergy gives any reason to suspect that a reaction may occur, a small initial dose may be given first. In any event, epinephrine hydrochloride 1:1,000 should always be available when the injection is made. The excretory urogram should be made by persons experienced with this method and during the entire procedure the patient should be watched for untoward reactions. Ocular, oral and intradermal tests to detect sensitivity to intravenously administered iodine compounds are not reliable since reactions are more often due to a direct vascular effect. The medium should be given slowly, with a pause after 1 or 2 cc. are

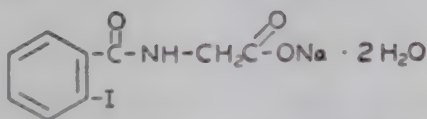


injected to note reaction. Care should be exercised to insure that all the solution is injected into the vein. Some clinicians apply pressure on the bladder region, releasing it immediately before the first exposure and renewing it until the next. Ordinarily, the first film is exposed about 10 minutes after injection and two subsequent pictures are taken at intervals of 15 or 20 minutes. A safe routine is to take roentgenograms 5, 15 and 45 minutes after injection of the drug. When renal function is impaired, the interval is proportionately longer. Side effects which may be encountered include flushing of the face and neck, urticaria, fall in blood pressure, diarrhea, generalized itching and weakness, nausea, vomiting, lacrimation, salivation, edema of the glottis, bouts of coughing, "tight feeling" or choking sensation and cyanosis. These symptoms usually disappear over varying periods of time, but fatalities have occurred.

The intravenous use of these drugs is contraindicated in patients with severe liver disorders, nephritis and severe uremia, and it should be used with caution in cases of active tuberculosis and of hyperthyroidism. Oral use of these compounds is contraindicated in acute disorders of the gastro-intestinal tract. Excretory urography should not be used routinely in all patients. Satisfactory urograms are rarely obtained when the maximum specific gravity of urine is 1.01. Further, this method may have to be checked with retrograde pyelography, and either or both methods closely correlated with the clinical findings. Injection of the medium into the kidney pelvis is most accurately gauged by using a manometer, but in default of this instrument, gravity or a syringe may be employed with care for retrograde pyelography. Because of reflex splanchnic stimulation, anuria has occurred, especially after bilateral examination. Excretory urography or retrograde pyelography may be repeated after an adequate interval.

The compounds may be used for venograms in the study of varicose veins.

**IODOHIPPURATE SODIUM.**—Hippuran (MALLINCKRODT).—Sodium *o*-iodohippurate dihydrate. This compound contains 35 per cent of iodine, or 39 per cent when calculated to the dried substance. The structural formula of iodohippurate sodium may be represented as follows:



**Physical Properties.**—Iodohippurate sodium is a white, crystalline salt with a faint odor and a soapy taste. It is very soluble in water, freely soluble in alcohol and soluble in dilute alkalis. A 5 per cent solution has a pH between 7.3 and 7.8.

**Actions and Uses.**—Iodohippurate sodium is proposed for use as a radiopaque agent for intravenous, oral or retrograde urography. When it is injected intravenously, there is no irritation at the site of injection and systemic reactions are unusual. A sensation of

generalized warmth is the most common side effect, nausea occurs occasionally and vomiting rarely.

Results with oral administration of the drug are less satisfactory but the percentage of successful pictures obtained is sufficiently high to make this method worthy of trial when intravenous or retrograde urography is not feasible. The objectionable taste of the compound usually does not militate against its ingestion. Toxic effects after oral administration have not been reported. Pictures are taken 60, 90, 120 and 150 minutes after oral administration.

This preparation gives satisfactory visualization when employed by the retrograde method for urethrograms, cystograms or pyelograms. There is little or no tissue irritation with effective concentrations.

See also the general statement on water-soluble organic iodine compounds for roentgenography.

**Dosage.**—For intravenous use, 25 cc. of a solution containing 12 Gm. of iodhippurate sodium, previously warmed to body temperature, is injected into the cubital vein. Young children are given proportionately smaller doses. For oral use, 12 Gm. of iodhippurate sodium is dissolved in 75 cc. of simple syrup. For children, 10 Gm. is employed. For retrograde use, iodhippurate sodium is employed in 15 to 20 per cent solution for pyelography or 3 to 5 per cent solution for cystography. The solution may be made either by diluting the ampul solution with sterile distilled water or by dissolving the crystals in distilled water, filtering and sterilizing by heat.

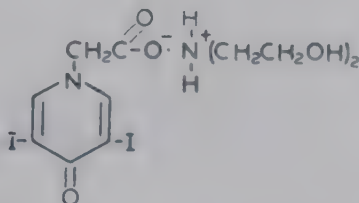
#### MALLINCKRODT CHEMICAL WORKS

**Crystals Hippuran:** 100 and 500 Gm. bottles.

**Solution Hippuran:** 25 cc. ampuls. A solution containing 0.48 Gm. of iodhippurate sodium in each cubic centimeter.

U. S. patent 2,135,474. U. S. trademark 314,577.

**IODOPYRACET.**—Diodrast (WINTHROP-STEARNs).—2,2'-Iminodiethanol salt of 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid.—Iodopyracet is prepared by neutralizing 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid in water with an equimolecular quantity of diethanolamine. The salt formed is very soluble in water and is not isolated. The structural formula of iodopyracet may be represented as follows.



**Actions and Uses.**—Iodopyracet is used as a contrast agent for intravenous urography. Side effects usually subside within a few minutes to an hour or so without special therapy, but skin erup-



tions may on rare occasions persist for several days. Iodopyracet lowers the blood pressure for about 2 hours; the slow return to normal pressure may be followed by a secondary rise. Respiration is stimulated.

See also the general statement on water-soluble organic iodine compounds for roentgenography.

**Dosage.**—Iodopyracet is usually administered intravenously in the form of an aqueous solution, each cubic centimeter of which contains 0.35 Gm. The solution is warmed to body temperature and 20 cc. are injected slowly, usually into the cubital veins. Children are given correspondingly smaller doses. It may be administered intramuscularly or subcutaneously in infants, children and adults with inaccessible or obliterated arm veins, and sometimes in uncooperative, restless patients. For subcutaneous injection the adult dose (20 cc.) is diluted with 80 cc. normal saline solution; 50 cc. of this mixture are injected subcutaneously over each scapula. For intramuscular injection the dose ranges from 10 to 20 cc. in children and from 20 to 30 cc. in adults. One-half of the amount is injected into each buttock. To prevent local discomfort a local anesthetic may be used if needed.

For cholangiography, the amount of iodopyracet injected varies within wide limits; from 15 to 100 cc. has been required for injection into the common bile duct.

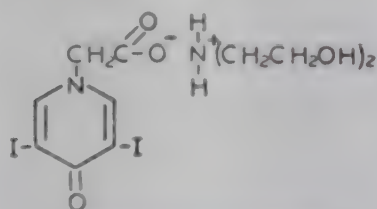
The dosage form listed below is identical to Iodopyracet Injection-U.S.P.

#### WINTHROP-STEARNs, INC.

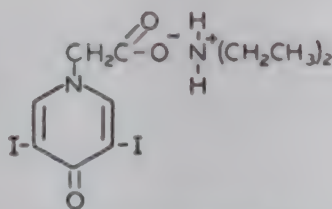
Solution Diodrast 35% W/V: 10 cc., 20 cc. and 30 cc. ampuls. A solution containing 0.35 Gm. of iodopyracet in each cubic centimeter.

U. S. trademark 312,451.

**IODOPYRACET COMPOUND.**—Diodrast Compound (WINTHROP-STEARNs).—A mixture of the 2,2'-iminodiethanol (commonly called diethanolamine) salt of 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid and the diethylamine salt of 3,5-diiodo-4-oxo-1(4H)pyridineacetic acid. Iodopyracet compound is prepared by neutralizing 3,5-diiodo-4-oxo-1-(4H)-pyridineacetic acid in water with appropriate quantities of diethanolamine and diethylamine. The salts formed are soluble in water and are not isolated. Their structural formulas may be represented as follows:



2,2'-Iminodiethanol salt  
of 3,5-diiodo-4-oxo-  
1(4H)-pyridineacetic  
acid



Diethylamine salt of  
3,5-Diiodo-4-oxo-  
1(4H)-pyridineacetic  
acid



**Physical Properties.**—The solution is a clear, pale yellow, odorless liquid with a bitter taste. It is neutral to litmus and is incompatible with mineral acids and salts of heavy metals.

**Actions and Uses.**—Iodopyracet compound is employed in solution for roentgenographic visualization of the urinary tract by intravenous injection or by direct injection into the renal pelvis through a ureteral catheter. It provides a large amount of iodine in a small volume of solution. This is particularly valuable for injection in obese subjects or for patients who cannot or will not co-operate in the preparation for excretion urography with iodopyracet injection. Roentgenograms should be taken at intervals of 5, 15 and 45 minutes after injection of the drug. Interpretation of delayed, incomplete or absent shadows is the same as when iodopyracet is employed.

See also the general statement on water-soluble organic iodine compounds for roentgenography.

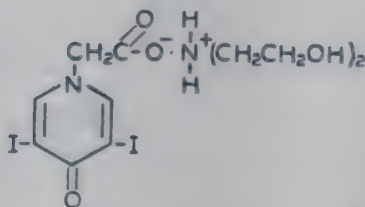
**Dosage.**—For excretion urography, iodopyracet compound is administered intravenously in sterile aqueous solution, the average dose for adults being 20 cc. Iodopyracet compound in the usual 50 per cent solution may be employed without dilution for retrograde pyelography. For economy, however, more dilute solutions are customarily used. When diluted with 12 cc. of sterile distilled water, a solution of 8 cc. of iodopyracet compound yields 20 cc. of 20 per cent concentration. Dilution of 5 cc. of iodopyracet compound solution with 15 cc. of sterile distilled water (final concentration 12.5 per cent) gives satisfactory pyelograms; this dilution is employed with excellent results in thin people. The volume of fluid generally required for retrograde examination in adults is 20 cc.

#### WINTHROP-STEARNs, INC.

Compound Solution Diodrast: 20 cc. ampuls.

U. S. trademark 312,451.

**IODOPYRACET CONCENTRATED.**—Diodrast Concentrated (WINTHROP-STEARNs).—Prepared by neutralizing 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid in water with an equimolecular quantity of diethanolamine. The salt formed is soluble in water, and is not isolated. The structural formula of the diethanolamine salt of 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid may be represented as follows:



**Actions and Uses.**—Iodopyracet concentrated is employed as a solution in a special diagnostic procedure for visualization of the heart, the ascending and descending aorta and branches, the supe-

rior vena cava, the pulmonary artery and branches, the coronary arteries and other structures of the heart and mediastinum. It has also been used for cholangiography by injection of a solution into the common bile duct. The technic in using this agent is complicated and requires accurate timing and teamwork between physician, patient and roentgenologist. The method consists in injecting the substance into the blood and taking roentgenograms simultaneously with the concentration of the opaque material in the cardiopulmonary system. A preliminary x-ray examination of the chest is necessary to obtain data for roentgenography. For accuracy it may be necessary to determine the circulation rate of the blood. Preliminary tests for renal function and sensitivity should be performed. To decrease incidence of nausea and vomiting the stomach should be empty. Premedication with a barbiturate is advisable and epinephrine is administered when there is a possibility of an allergic reaction or low blood pressure.

Side effects include dizziness, nausea, vomiting, sense of intense warmth, sweating, pallor, hypotension, transient pain at the site of injection, headache, fever, chills and cyanosis. Delayed reactions may occur. Contraindications include idiosyncrasy, hepatic disease, nephritis and hyperthyroidism. The drug should be used cautiously in the presence of heart disease and circulatory failure and never in patients who are critically ill or in collapse. This technic may be dangerous when used casually or by persons who are inexperienced. In skilled hands the drug causes few untoward reactions. This agent is sufficiently stable to permit boiling for a short time if necessary, although the product is marketed in sterile form.

*Iodopyracet concentrated should not be used for excretion urography. Because of the possibility of toxicity, it should be used intravenously only in cases which present difficult diagnostic problems.*

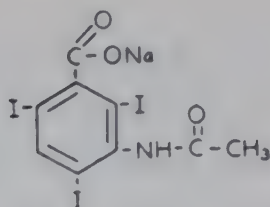
**Dosage.**—The amount varies according to the diameter of the chest, the size of existent pulmonary congestion and body weight. For cardiopulmonary visualization 40 to 45 cc. of a solution may be injected intravenously. When visualization of the pulmonary circulation is desired, 30 to 35 cc. may be sufficient. If the intravenous injection must be repeated, 15 minutes should elapse between injections. The duration of injection should be from 1½ to 2 seconds. Injection of the material into the tissue outside the vein causes irritation. If crystals are present, warm solution to body temperature before using.

#### WINTHROP-STEARNs, INC.

Concentrated Solution Diodrast 70% W/V: 20 cc. ampuls and 50 cc. ampuls. An aqueous solution containing 70 per cent of the diethanolamine salt of 3,5-diiodo-4-oxo-1(4H)-pyridineacetic acid.

**SODIUM ACETRIZOATE.**—Urokon Sodium (MALLINCKRODT).—Sodium 3-acetylamino-2,4,6-triiodobenzoate.—Sodium acetrizoate is prepared by dissolving the free acid in dilute sodium hydroxide. The salt is not isolated from the solution. The structural formula of sodium acetrizoate may be represented as follows:





**Physical Properties.**—The solutions are clear and practically colorless. The pH is between 7.0 and 7.4.

**Actions and Uses.**—Sodium acetrizate is employed as a contrast medium for excretory urography, retrograde pyelography, nephrography, translumbar arteriography and angiocardiology. It should be employed only in these procedures until satisfactory technic has been developed for the visualization of other structures. Although it contains a greater amount of iodine than do other similar agents, studies thus far indicate that it is less toxic.

See also the general statement on water-soluble organic iodine compounds for roentgenography.

**Dosage.**—For intravenous urography, 25 cc. of a 30 per cent solution is considered adequate for adults and children over 4 years of age. Where greater density is desired, 25 cc. of the 70 per cent solution is recommended, and for children under 4 years of age a dose of 500 mg. of sodium acetrizate per kilogram of body weight is usually employed (about 0.7 cc. of sodium acetrizate per kilogram of body weight). In any case, the total time for injection should not be less than 30 seconds and need not be more than 1 minute. Injection should be discontinued immediately in the presence of alarming symptoms. In contrast to the instructions in the general statement on water-soluble organic iodine compounds, the best results are obtained by making exposures at 5, 10 and 15 minutes after the injection.

For retrograde pyelography the dilute solution employed may contain 30 per cent or less of sodium acetrizate, depending on the degree of contrast desired. Bilateral ureteral injection is usually tolerated. Approximately 25 cc. are needed for bilateral injections; 15 cc. for unilateral pyelograms. Usually 5 to 6 cc. are required for each exposure. Neither excretory nor retrograde pyelography should be repeated within 24 hours.

For translumbar arteriography in adults and children 12 years of age or over, 10 to 15 cc. of a 70 per cent solution is sufficient. In children under 12 years of age, a dose proportionate to age is used.

For angiocardiology and nephrography in adults and in children 12 years of age or over, 40 to 50 cc. of a 70 per cent solution is adequate. For children under 12 years of age, a dose proportionate to age is given. For infants and small children, a dose of 1 cc. of the 70 per cent solution per kilogram of body weight is employed.

MALLINCKRODT CHEMICAL WORKS

Solution Urokon Sodium 30%: 25 cc. ampuls and 25 cc. vials. A

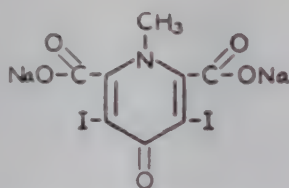


solution containing 0.3 Gm. of sodium acetrizoate in each cubic centimeter. Stabilized with 0.05 mg. of calcium ethylenediamine-tetraacetate and buffered with 0.12 mg. of sodium biphosphate in each cubic centimeter.

**Solution Urokon Sodium 70%:** 25 cc. ampuls and 50 cc. vials. A solution containing 0.7 Gm. of sodium acetrizoate in each cubic centimeter. Stabilized with 0.12 mg. of calcium ethylenediamine-tetraacetate and buffered with 0.12 mg. of sodium biphosphate in each cubic centimeter.

U. S. patent 2,611,786. U. S. trademark 519,732.

**SODIUM IODOMETHAMATE-U.S.P.—Neo-Iopax (SCHERING).—**Disodium 1-methyl-3,5-diiodo-4-pyridone-2,6-dicarboxylate.—Disodium 1-methyl-3,5-diiodochelidamate.—“Sodium Iodomethamate, dried for 24 hours over sulfuric acid in a vacuum desiccator, contains not less than 50.5 per cent and not more than 52.5 per cent of I, corresponding to not less than 98 per cent of  $C_8H_3I_2NNa_2O_5$ .” *U.S.P.* The structural formula of sodium iodomethamate may be represented as follows:



**Physical Properties.**—Sodium iodomethamate occurs as a white, odorless powder. One gram of sodium iodomethamate dissolves in about 1 cc. of water and in about 100 cc. of alcohol. It is insoluble in ether and in chloroform.

**Actions and Uses.**—Sodium iodomethamate is used as a contrast medium in intravenous urography and retrograde pyelography. It is employed in specified concentration for angiocardiology, but should not be used for cerebral angiography until evidence for this procedure is more complete. Systemic reactions are uncommon and are usually mild and fleeting. In some cases there is severe pain radiating from the arm to the shoulder; this usually disappears on completion of the injection but it may persist for a variable period. The pain may be relieved by local applications of heat and the administration of an analgesic when necessary. Fluid intake should be restricted for about 12 hours prior to the examination. If only anatomic information is desired, it is usually sufficient to take a single roentgenogram from 10 to 20 minutes after injection. In other cases, a series of roentgenograms is taken at intervals of 5, 15 and 30 minutes after injection. It is advisable to take a film over the urinary bladder area when making the roentgenogram 30 minutes after the injection. If the first plates show that little of the drug has been excreted, the kidneys are functioning poorly, and several hours should be allowed to elapse, during which plates should be made at intervals.

See also the general statement on water-soluble organic iodine compounds for roentgenography.

**Dosage.**—For intravenous urography either a 50 or a 75 per cent solution of sodium iodomethamate may be injected, the quantity depending on the conditions required for adequate roentgen visualization of those structures. The average adult patient will require 20 cc. of the 50 per cent solution, and children under 12 will require 10 to 15 cc. of the 50 per cent solution. For retrograde pyelography, the 50 or 75 per cent solution is diluted with sterile distilled water to 20 per cent. About 15 cc. of a 20 per cent solution usually is sufficient for unilateral and 25 cc. for bilateral administration. For angiocardiology, the 75 per cent solution should be employed in accordance with specialized roentgenologic technics. Cardiac angiography must be undertaken with caution if at all in chronic pulmonary disease, especially pulmonary fibrosis with emphysema, and in cyanotic infants. Congestive heart failure, unless terminally severe, is not a contraindication.

Solutions of sodium iodomethamate should be warmed to body temperature prior to intravenous administration, and the usual precautions should be taken to avoid sensitivity reactions to the agent.

For rapid intravenous injection of the 50 or 75 per cent solution, the solution is prewarmed to body temperature. A 19 or 20 gauge needle is used and all precautions are observed to assure the needle being well within the lumen of the vein; then 1 cc. of the solution is injected. After waiting 45 to 60 seconds to detect any possible sensitivity reaction, the remainder of the solution is injected rapidly within 1 minute, preferably within 30 seconds. Immediately after the needle is withdrawn, the arm is held above and perpendicular to the trunk for a few moments to facilitate venous drainage.

#### SCHERING CORPORATION

**Solution Neo-lopax 50%:** 20 and 30 cc. ampuls. An aqueous solution containing 0.5 Gm. of sodium iodomethamate in each cubic centimeter.

**Solution Neo-lopax 75%:** 20 cc. ampuls and, for angiocardiology, 50 cc. ampuls. An aqueous solution containing 0.75 Gm. of sodium iodomethamate in each cubic centimeter.

U. S. trademark 297,925.

## Diuretics

Diuretics are employed to promote the excretion of water and sodium chloride that have accumulated in excess in the interstitial tissues or serous cavities. Such accumulations are associated chiefly with affections of the heart, kidneys or liver. The diuretic agents currently available have their greatest usefulness in the adjunctive treatment of congestive heart failure and portal cirrhosis of the liver. Their effectiveness is variable in nephrotic edema or the edema associated with chronic nephritis of the glomerular or vascular type. They are virtually ineffective and even may be harmful in the treatment of acute nephritis. In all cases in which the edema is attributable to renal disease, diuretic agents must be used cautiously, particularly when there is nitrogen retention.

The organic mercurials are the most powerful diuretics now available. Their effectiveness is increased and the disagreeable side effects are reduced when they are combined with theophylline or sodium thioglycollate. For this reason, the mercurials which are not thus combined have largely dropped out of use.

The once popular xanthine derivatives when used alone are relatively weak and unpredictable diuretics. Now they rarely are employed primarily for their diuretic effect, except when use of mercurials is contraindicated or when it is desirable to give a diuretic orally.

Both the mercurials and the xanthines act upon the kidney tubules to retard the reabsorption of sodium and, concurrently, the reabsorption of water. Other measures designed to reduce the body stores of sodium serve to increase the effectiveness of the diuretic drugs. Such measures include a low salt diet and/or the administration of cation exchange resins to reduce the absorption of sodium from the gastro-intestinal tract and the administration of acid-producing salts, such as ammonium chloride, to promote sodium excretion by the kidney. Sodium depletion also may be accomplished by administering salt-free fluids either by mouth or parenterally, though these measures must be used cautiously to avoid overloading the circulation. When sodium stores have been reduced by other measures, rapid or prolonged diuresis from repeated injections of mercurials may unduly deplete the body of sodium and cause the condition described as low salt syndrome.

Urea which is still employed occasionally for its diuretic effect has an extremely disagreeable taste and may cause gastro-intestinal disturbances. It is a less reliable agent than the mercurials, but



it may have adjunctive usefulness provided the excretory function of the kidneys is not impaired.

When edema is attributable to hypoalbuminemia, diuresis may be obtained by intravenous injections of normal human serum albumin (salt-poor).

## MERCURY COMPOUNDS

The principal mercurial diuretics are similar in structure. They are primarily methoxy-mercuripropyl derivatives of organic acids; frequently the amide derivatives of dibasic acids. Mercumatilin differs slightly in that it is a monobasic acid and its mercurated allyl group is attached directly to a carbon atom rather than to a nitrogen atom. The local irritant action of these compounds is diminished and the diuretic efficiency increased by the addition of theophylline or sodium thioglycollate. At present most mercury diuretics are available in combination with theophylline. Acid-producing diuretics, such as ammonium chloride, administered orally prior to injection of the mercurials, increase the diuretic effect of the latter.

Mercurial diuretics are proposed for use in cardiac edema, nephrotic edema, ascites of liver disease and in carefully selected cases of subacute and chronic nephritis. The diuresis from the mercurials eliminates not only water but also sodium, and thus decreases the body's capacity to retain fluid. In cardiac disease the diuresis may relieve symptoms such as dyspnea even though manifest edema is not present.

Mercurials are contraindicated in acute nephritis and should be used with caution in chronic kidney disease. Since mercury gives rise in sensitive patients to side effects such as stomatitis, gastric disturbances, vertigo, febrile reactions and cutaneous eruptions, initial tests and careful regulation of dosage are suggested when mercury diuretics are used. However, some patients may be sensitive to one mercurial, yet tolerate another satisfactorily. Sudden fatalities have been reported following the use of mercurial diuretics injected intravenously and although these mishaps are rare, caution should be exercised. Since the evidence indicates that ventricular arrhythmia is the mechanism of these fatalities, special precautions should be taken with patients who already are candidates for such arrhythmia, for example, patients with frequent ventricular extrasystoles, heavily digitalized patients and those with recent myocardial infarction.

During prolonged administration of mercurial diuretics the urine should be examined periodically for albumin, casts and blood cells.

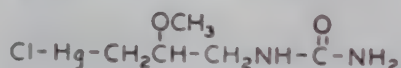
Intervals between the repeated injections which are used to maintain freedom from cardiac edema are based on changes in body weight. In the absence of a diuretic response, repeated injections are contraindicated. Especially in cases where sodium chloride is restricted in the diet, prolonged diuresis from repeated injections of mercurials may unduly deplete the body of sodium and cause symptoms of weakness, collapse, hypotension, hemoconcentration

and azotemia. These symptoms can be promptly alleviated by administration of sodium salts.

Many of these diuretics are effective and relatively safe when administered by intramuscular injection; some may be given subcutaneously.

The mercurial diuretics may be given orally in tablet form. However, oral use can supplant injections in only a very small percentage of cases since this method is much less effective in producing diuresis and may cause symptoms of gastro-intestinal irritation. In some cases the necessity of frequent injection can be diminished by oral medication. These drugs can also be given as rectal suppositories, but the effect produced is mild and the diuresis usually sufficient to control only the milder cases. Rectal irritation sufficient to make other methods of administration preferable occurs fairly frequently.

**CHLORMERODRIN.**—**Neohydrin** (LAKESIDE).—[3-(Chloromercuri)-2-methoxypropyl]urea.—The structural formula of chlormerodrin may be represented as follows:



**Physical Properties.**—Chlormerodrin is a white, odorless powder with a bitter, metallic taste. It is very soluble in sodium hydroxide T.S. and very slightly soluble in chloroform. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 0.56 Gm. in alcohol, 1.1 Gm. in methyl alcohol and 1.1 Gm. in water. Chlormerodrin is stable to light and air. The pH of a 0.5 per cent solution is 4.3 to 5.0.

**Actions and Uses.**—Chlormerodrin is a mercurial diuretic compound chemically related to meralluride. It is more effective orally than previously introduced mercurial diuretics that can be administered by this route. It is thus useful for oral, mercurial, diuretic therapy in the management of recurring cardiac and nephrotic edema, ascites of liver disease and in carefully selected cases of subacute and chronic nephritis. Chlormerodrin may supplant the need for injection therapy in some patients, but in others parenteral treatment may be required to replace or supplement oral medication.

**Dosage.**—Chlormerodrin is administered orally. The average daily dose for adults ranges from 18.3 mg. (equivalent to 10 mg. of mercury) to 73.2 mg. (40 mg. of mercury), depending upon the severity of edema or circulatory failure. The dosage for children is adjusted in proportion to body weight. Reduction of dosage or withdrawal of medication may be necessary to eliminate side effects.

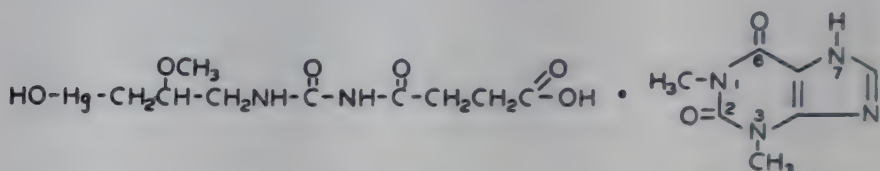
LAKESIDE LABORATORIES, INC.

**Tablets Neohydrin:** Each tablet contains 18.3 mg. of chlormerodrin (equivalent to 10 mg. of mercury).



**MERALLURIDE-U.S.P. — Mercurhydrin (LAKESIDE).** — 1-(3'-Hydroxymercuri-2'-methoxypropyl)-3-succinylurea and theophylline — "Meralluride consists of methoxyoxymercuripropylsuccinylurea (the mercuri compound,  $C_9H_{16}HgN_2O_6$ , mol. wt. 448.84), and of theophylline in approximately molecular proportions. Meralluride, dried at  $105^\circ$  for 3 hours, contains not less than 94 per cent and not more than 106 per cent of the labeled amounts of the mercuri compound and of anhydrous theophylline ( $C_7H_8N_4O_2$ )."  
*U.S.P.*

The structural formula of meralluride may be represented as follows:



**Physical Properties.**—Meralluride is a white to faintly yellow powder. It is slowly affected by light, and its solution is acid to litmus paper.

**Actions and Uses.**—Meralluride is a mercurial diuretic used for the preparation of solutions of its sodium salt for injection. The drug, as the non-reacted acid with sodium bicarbonate, is utilized for rectal administration in the form of suppositories. The latter are suitable as a supplement to parenteral injections of the sodium salt in order to prolong the edema-free period. Suppositories alone may control mild cases of edema. The indications and precautions are the same as for other mercurials. See the general statement on mercury compounds.

**Dosage.**—Rectally, a suppository containing 0.6 Gm. of meralluride is given daily; as a supplementary measure to parenteral administration one suppository may be given daily beginning one to three days after injection.

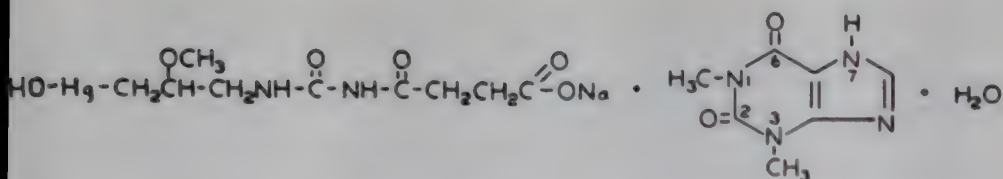
LAKESIDE LABORATORIES, INC.

**Suppositories Mercurhydrin:** 0.6 Gm. of meralluride (equivalent to 0.19 Gm. of mercury). Buffered with 80 mg. of sodium bicarbonate.

U. S. trademark 506,726.

**MERALLURIDE SODIUM. — Mercurhydrin Sodium (LAKESIDE).** — Sodium 1-(3'-hydroxymercuri-2'-methoxypropyl)-3-succinylurea and theophylline. — Meralluride sodium consists of sodium methoxyoximercuripropylsuccinylurea (the mercuri compound,  $C_9H_{15}HgN_2NaO_6$ , mol. wt. 470.83) and of theophylline-U.S.P. in approximately molecular proportions. It is prepared by adding just enough sodium hydroxide solution to meralluride to effect solution. The salt is not isolated. An excess over one mole of theophylline may be added. The structural formula of meralluride sodium may be represented as follows:





**Actions and Uses.**—Meralluride sodium solution is a mercurial diuretic proposed for use in the edema of cardiorenal disease and of nephrosis, ascites of liver disease and other conditions in which a mercurial diuretic is indicated.

It is well tolerated systemically and when given intramuscularly seldom causes pain at the site of injection. It is rapidly absorbed following intramuscular injection. It is also administered by intravenous injection. The drug is also effective when administered by subcutaneous injection, although painful local reactions have been noted in some patients.

For contraindications and cautions, see the general statement on mercury compounds.

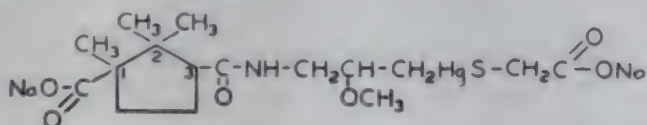
**Dosage.**—Depending on the condition of the patient and route and frequency of administration, the dose of meralluride sodium (in a solution containing 0.13 Gm. of meralluride sodium and 10 mg. of theophylline per cubic centimeter) varies from 1 to 2 cc. In view of occasional cases of idiosyncrasy to mercurials, the initial dose should be 0.5 cc. or less. Subsequent injections may be given twice weekly as indicated by the condition of the patient. One investigator has recommended smaller doses repeated at shorter intervals and emphasizes the importance of observing water balance daily instead of weekly.

LAKESIDE LABORATORIES, INC.

**Solution Mercuhydrin Sodium:** 1 cc. and 2 cc. ampuls and 10 cc. vials. A solution containing 0.13 Gm. of meralluride sodium (equivalent to 39 mg. of mercury) and 10 mg. of excess theophylline in each cubic centimeter. The 10 cc. vials are preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

U. S. patent 2,208,941.

**MERCAPTOMERIN SODIUM.**—Thiomerin Sodium (WYETH).—Disodium N-[3-(Carboxymethylmercaptomercuri)-2-methoxypropyl]- $\alpha$ -camphoramate.—The structural formula of mercaptomerin sodium may be represented as follows:



**Physical Properties.**—Mercaptomerin sodium is a hygroscopic, white solid. It is freely soluble in water, soluble in alcohol, very slightly soluble in ether and practically insoluble in benzene and chloroform.

**Actions and Uses.**—Mercaptomerin sodium is an effective mercurial diuretic which produces much less local irritation on injection.

tion than other organomercurial compounds used for this purpose. It is less toxic to the heart than the previously employed mercurial diuretics and shares the other actions of these compounds, including the potential toxic effects of mercury. Preliminary acidification of the urine also sometimes enhances its diuretic effect. See the general statement on mercury compounds.

Mercaptomerin sodium is contraindicated in advanced chronic nephritis and acute renal disease. Care must be taken in its use with drastic sodium chloride restriction to avoid salt depletion from copious diuresis.

**Dosage.**—Mercaptomerin sodium is administered by subcutaneous injection in the form of a solution, readily prepared from the dry form of the drug, in a concentration of about 0.13 Gm. per cubic centimeter of sterile water (13 per cent). Each cubic centimeter of this solution contains 0.13 Gm. of mercaptomerin sodium, equivalent to 43 mg. of mercury.

Mercaptomerin sodium is sufficiently free of local irritant effects to warrant recommendation for subcutaneous injection although painful local reactions have been noted in some patients; by this route it produces diuretic effects similar to those of equivalent doses of other mercurial diuretics administered intravenously. Care must be taken to place the injection beneath the subcutaneous fat, to make repeated injections at different sites and to avoid edematous areas. Extreme emaciation may make intramuscular injection preferable.

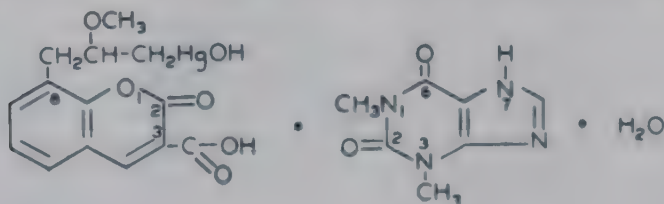
The dosage of the 13 per cent solution ranges from 0.5 to 2 cc. subcutaneously, depending on the requirements of the individual patient. The drug is sensitive to heat, and should be kept under refrigeration. The solution should be discarded on appearance of turbidity.

#### WYETH LABORATORIES, INC.

**Powder Thiomerin Sodium:** 1.4 Gm. and 4.2 Gm. vials. When made up with 10 cc. and 30 cc. of sterile water, respectively, a 13 per cent solution is obtained, each cubic centimeter of which contains 0.13 Gm. of mercaptomerin sodium (equivalent to 43 mg. of mercury).

U. S. trademark 436,086.

**MERCUMATILIN.**—**Cumertilin (ENDO).**—8-(2'-Methoxy-3'-hydroxymercuripropyl)coumarin-3-carboxylic acid (mercumallylic acid) and theophylline.—Mercumatilin consists of mercumallylic acid (the mercuri compound  $C_{14}H_{14}HgO_6$ , mol. wt. 478.86) and of theophylline-U.S.P. in approximately molecular proportions. The structural formula of mercumatilin may be represented as follows:





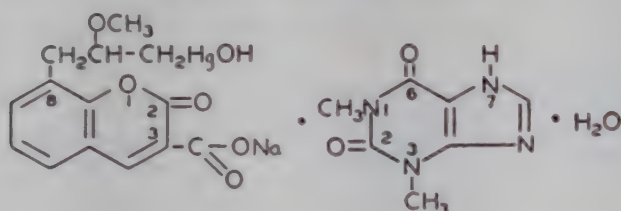
**Actions and Uses.**—Mercumatilin is used as a diuretic for the same purposes as other orally effective mercury-theophylline compounds. It should be employed chiefly as an adjunct to parenteral injection of the sodium salt. See the general statement on mercury compounds and the monograph on mercumatilin sodium.

**Dosage.**—The average daily dose for adults is 67 to 134 mg. Some patients may require 200 to 270 mg. daily to reduce the frequency of injections (administered as the sodium salt) needed to maintain an edema-free state.

#### ENDO PRODUCTS, INC.

**Tablets Cumertilin:** 67 mg. Each tablet contains 67 mg. of mercumatilin (equivalent to 20 mg. of mercury).

**MERCUMATILIN SODIUM.**—Cumertilin Sodium (ENDO).—Sodium 8-(2'-methoxy-3'-hydroxymercuripropyl)coumarin-3-carbonate (sodium mercumallylate) and theophylline.—Mercumatilin sodium consists of sodium mercumallylate (the mercuri compound,  $C_{14}H_{13}HgNaO_6$ , mol. wt. 500.85) and of theophylline-U.S.P. in approximately molecular proportions. It is prepared by adding just enough sodium hydroxide solution to mercumatilin to effect solution. The salt is not isolated. An excess over one mole of theophylline may be added. The structural formula of mercumatilin sodium may be represented as follows:



**Actions and Uses.**—Mercumatilin sodium produces the same diuretic effect as other mercury-theophylline compounds, from which it differs slightly only in chemical structure. Its injection causes local irritation similar to that produced by the other organic mercurial diuretics which are suitable only for intramuscular or intravenous injection. See also general statement on mercury compounds.

**Dosage.**—Mercumatilin sodium is administered either intramuscularly or intravenously, preferably the former. An initial dose of not more than 0.5 cc. (containing 0.132 Gm. per 1 cc.) is recommended. Unless there is idiosyncrasy the subsequent average dosage recommended is 2 cc. intramuscularly, or 1 to 2 cc. intravenously, at biweekly intervals. Shorter or longer intervals may be used in accordance with the degree of edema or dehydration present. Injections should be made at different sites to avoid undue local irritation. Mercumatilin sodium should be employed with the same precautions as other mercurial diuretics.

#### ENDO PRODUCTS, INC.

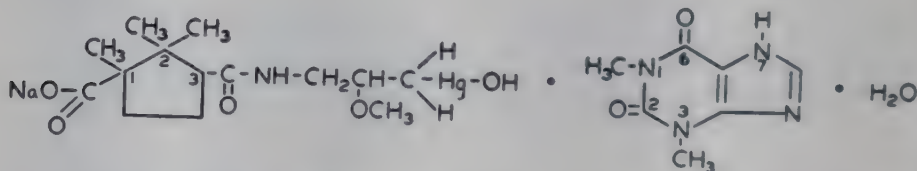
**Solution Cumertilin Sodium:** 1 and 2 cc. ampuls and 10 cc. vials.



An aqueous solution containing 0.132 Gm. of mercumatilin sodium (equivalent to 39 mg. of mercury) and 11 mg. of excess theophylline in each cubic centimeter. The 10 cc. vials are preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

**Solution Cumertilin Sodium with Benzyl Alcohol 2%:** 10 cc. vials. An aqueous solution containing 0.132 Gm. of mercumatilin sodium (equivalent to 39 mg. of mercury) and 11 mg. of excess theophylline in each cubic centimeter.

**MERCUROPHYLLINE SODIUM.**—**Mercuzanthin (CAMPBELL).**—Sodium  $N^3$ -[(3-hydroxymercuri)-2-methoxypropyl]- $\alpha$ -camphoramate and theophylline.—Sodium  $\beta$ -methoxy- $\gamma$ -hydroxymercuripropylamide of 1,2,2-trimethylcyclopentane-1,3-dicarboxylate and theophylline.—“Mercuriophylline [sodium] consists of the sodium salt of  $\beta$ -methoxy- $\gamma$ -hydroxymercuripropylamide of trimethylcyclopentanedicarboxylic acid (the mercuri compound,  $C_{14}H_{24}HgNNaO_5$ , mol. wt. 509.95), and of theophylline, in approximately molecular proportions. Dried at  $105^\circ$  for 4 hours, it contains not less than 94 per cent and not more than 106 per cent of the labeled amount of the mercuri compound ( $C_{14}H_{24}HgNNaO_5$ ) and of anhydrous theophylline ( $C_7H_8N_4O_2$ ).” *U.S.P.* The solution for injection may contain an excess over one mol. of theophylline. The structural formula of mercuriophylline may be represented as follows:



**Physical Properties.**—Mercuriophylline sodium occurs as a white or slightly yellow, odorless powder. It is moderately hygroscopic and slowly darkens on exposure to light. Its solutions are alkaline to litmus paper. One gram of mercuriophylline sodium dissolves in about 5 ml. of water. It is soluble in alcohol, but insoluble in ether and in mineral oils.

**Actions and Uses.**—Mercuriophylline sodium is a potent diuretic. It is less toxic and more active than the purine-free mercurial diuretics. When theophylline is combined with the mercurial, sloughs and venous thromboses occur with less frequency and severity. The presence of theophylline enhances the rate and completeness of absorption, so that the drug is effective and well tolerated by intramuscular as well as intravenous administration.

Mercuriophylline sodium is used to remove excess fluid in edema of congestive heart failure, nephrosis and cirrhosis of the liver with ascites. It is contraindicated in advanced chronic nephritis without edema and in acute renal disease.

Diuresis develops slowly following oral administration of mercuriophylline and does not reach its peak for 48 hours. The total diuretic response may approach that produced by intravenous in-

jection. Reactions to orally administered mercurophylline include gastro-intestinal irritation, and possible kidney damage after prolonged use.

**Dosage.**—Solutions of mercurophylline containing 0.135 Gm. to 0.155 Gm. per cubic centimeter, stabilized with an excess of theophylline, are employed for intramuscular injection. Benzyl alcohol is occasionally added to lessen the pain of intramuscular injection. To discover intolerance to the preparation, a much smaller trial dose should be injected. Caution must be exercised to prevent leakage into the subcutaneous tissue.

Intravenous injection may be carried out with similar concentrations of the drug, but more dilute concentrations not containing benzyl alcohol are preferred, since unpleasant side effects may occur with the concentrated solution.

When maximum diuresis is desired in patients with massive edema, approximately 275 mg. administered at one time will usually produce a response comparable to that obtained with repeated injections. In severe cases, reaccumulation of the dropsical fluid may be partly or entirely controlled with 60 to 110 mg. daily; in milder cases with occult edema, 60 to 110 mg., three times daily on 2 or 3 successive days is recommended. Oral dosage for maintenance is 100 to 200 mg. daily.

#### CAMPBELL PHARMACEUTICAL COMPANY

**Enteric Coated Tablets Mercuzanthin (Sodium):** 0.1 Gm. (equivalent to 28 mg. of mercury).

**Solution Mercuzanthin (Sodium):** 1 cc. and 2 cc. ampuls. A solution containing 0.135 Gm. of mercurophylline sodium (equivalent to 38 mg. of mercury) in each cubic centimeter.

U. S. patent 2,117,901. U. S. trademark 418,384.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Mercurophylline Sodium:** Bulk; for manufacturing use.

#### FLINT, EATON & COMPANY

**Solution Mercurophylline (Sodium):** 1 cc. and 2 cc. ampuls. A solution containing 0.15 Gm. of mercurophylline (equivalent to 43 mg. of mercury) in each cubic centimeter.

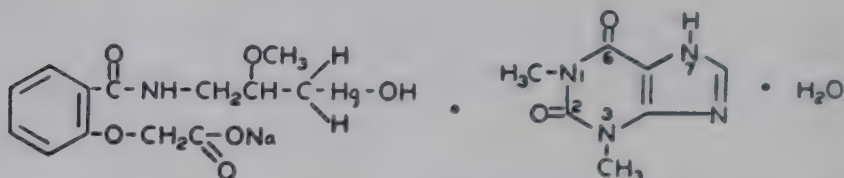
#### LINCOLN LABORATORIES, INC.

**Solution Mercurophylline (Sodium):** 1 cc. and 2 cc. ampuls. A solution containing 0.14 mg. of mercurophylline sodium (equivalent to 39 mg. of mercury) in each cubic centimeter.

**MERSALYL SODIUM AND THEOPHYLLINE.**—Mersalyn (Kirk). — Salyrgan-Theophylline (WINTHIROP-STEARNs). — Sodium *o*-[(3-hydroxymercuri-2-methoxypropyl) carbamyl]phenoxyacetate and theophylline.—Mersalyl sodium and theophylline consists of two parts by weight of the sodium salt of *o*-[(3-hydroxymercuri-2-methoxypropyl) carbamyl]phenoxyacetic acid (the mercuri compound,  $C_{13}H_{16}HgNNaO_6$ , mol. wt. 505.87) to one part by weight



of theophylline-U.S.P. ( $C_7H_8N_4O_2 \cdot H_2O$ ). The structural formulas of mersalyl sodium and of theophylline may be represented as follows:



**Physical Properties.**—Mersalyl and theophylline each occur as a white or almost white, crystalline powder. They are odorless and have a bitter taste. Theophylline is stable in air. Mersalyl is somewhat deliquescent and is decomposed gradually by light; its solutions are alkaline to litmus paper. One gram of mersalyl dissolves in about 1 cc. of water; 1 Gm. of theophylline dissolves in about 120 cc. of water.

**Actions and Uses.**—Mersalyl sodium and theophylline has been demonstrated to produce less local reaction on intramuscular or intravenous injection than mersalyl sodium alone and to be more effective. The more rapid resorption of mersalyl sodium in combination with theophylline accelerates diuresis and, by preventing the deposition of mercury, improves the local tolerance. Mersalyl sodium and theophylline is proposed as a diuretic for dropsy in cardiorenal disease and in nephrosis, ascites of liver diseases and other conditions. It is contraindicated in acute nephritis and chronic kidney disease without edema and in intestinal inflammation with diarrhea. For side effects and cautions, see general statement on mercury compounds.

**Dosage.**—The adult dose of 0.2 Gm. of mersalyl sodium and 0.1 Gm. of theophylline may be injected intramuscularly or intravenously. For susceptibility, test the patient with one-half of the recommended dose. If the test dose is well tolerated, the recommended dose may be given on the following day. In some cases this dose may have to be doubled for the full effect. Injections are not usually given more frequently than every 3 or 4 days. After relief of the dropsy, recurrences can often be prevented by occasional injections. One dose of about 0.3 Gm. may be given in the morning after breakfast and repeated in 4 to 5 days if required. As an adjunct to parenteral medication, about 0.1 Gm. may be given orally every day for 1 or 2 weeks, but in such instances rest periods of 1 or 2 weeks should intervene between courses of treatment. For children the dosage should be reduced by one-half.

#### C. F. KIRK COMPANY

**Solution Mersalyn with Benzyl Alcohol 2%:** 2 cc. ampuls and 10 cc. vials. A solution containing 0.1 Gm. of mersalyl (equivalent to 40 mg. of mercury) and 50 mg. of theophylline in each cubic centimeter.



## S. E. MASSENGILL COMPANY

**Solution Mersalyl and Theophylline:** 2 cc. ampuls. A solution containing 0.1 Gm. mersalyl (equivalent to 39.6 mg. mercury) and 50 mg. of theophylline in each cubic centimeter.

## WINTHROP-STEARNs, INC.

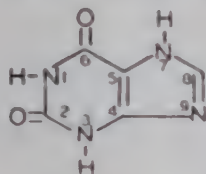
**Solution Salyrgan (Sodium) Theophylline:** 1 cc. and 2 cc. ampuls and 1 cc. Ampins. A solution containing 0.1 Gm. mersalyl sodium (equivalent to 40 mg. of mercury) and 50 mg. theophylline in each cubic centimeter.

**Enteric Coated Tablets Salyrgan (Sodium) Theophylline:** Each tablet contains 80 mg. mersalyl sodium (equivalent to 32 mg. of mercury) and 40 mg. theophylline.

U. S. patent 2,213,457. U. S. trademark 188,515.

## XANTHINE DERIVATIVES

Caffeine, theobromine and theophylline are methylxanthines, derived from xanthine by the introduction of two or three methyl radicals at the corresponding number of heterocyclic nitrogen atoms. As these may occupy various positions in the xanthine nucleus, a number of methylxanthines exist, naturally and by synthesis, differing quantitatively in pharmacologic activity. Those named, however, are the only ones of therapeutic importance; caffeine is 1,3,7-trimethylxanthine, theobromine is 3,7-dimethylxanthine and theophylline is 1,3-dimethylxanthine. The structural formula of xanthine may be represented as follows:



Caffeine is usually obtained from tea or coffee; theobromine is obtained from cacao, or is made synthetically. Theophylline occurs in nature but in amounts too small to be commercially available, so it is prepared synthetically.

Theobromine and theophylline surpass caffeine in their diuretic, and perhaps in cardiac and muscular actions. They are, therefore, generally preferred in cardiac edemas, etc., since they are equally or more effective, more prompt and largely avoid the unpleasant side effects (insomnia, nervousness, gastric disturbance) which often interfere with the use of caffeine in adequate doses. This freedom from side effects holds true particularly for theobromine. Theophylline surpasses theobromine in diuretic efficacy, but its action is probably not so lasting; it may produce gastric disturbances or renal irritation. If central stimulation is desired, caffeine should be used. In recent years, diuresis by administration of the xanthine derivatives in combination with the more effective mercurial

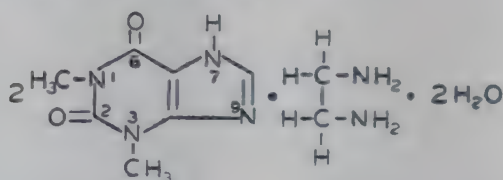
diuretics has superseded the use of the methylxanthines alone. The clinical use of theobromine has been largely abandoned in favor of the slightly more active theophylline.

The slight solubility of theobromine and theophylline limits their usefulness. They are therefore used almost exclusively in the form of the readily soluble double salts, which they form with a number of compounds: theobromine and sodium salicylate-N.F., theobromine and sodium acetate-U.S.P., theophylline and sodium acetate-U.S.P. and aminophylline-U.S.P. (theophylline ethylenediamine).

There is no reason to suppose that the particular salt used to procure the solubility has any material influence on the action. The dosage of these added compounds is also generally too small to produce therapeutic effects. It may, therefore, be assumed that the various preparations are equivalent. There is no basis for claims that the xanthines effectively control arterial hypertension. Increased coronary blood flow which follows rather than precedes myocardial stimulation cannot be considered an adequate basis to support claims for use of the drug in coronary disease or angina pectoris.

### Theophylline Compounds

**AMINOPHYLLINE-U.S.P.** — Theophylline ethylenediamine. — "Aminophylline contains not less than 75 per cent and not more than 82 per cent of anhydrous theophylline ( $C_7H_8N_4O_2$ ), and not less than 12.3 per cent and not more than 13.8 per cent of ethylenediamine ( $C_2H_8N_2$ )."  
*U.S.P.* The structural formula of aminophylline may be represented as follows:



**Physical Properties.**—Aminophylline occurs as white or slightly yellowish granules with a slight ammoniacal odor and a bitter taste. One gram is soluble in about 5 cc. of water but insoluble in alcohol and in ether.

**Actions and Uses.**—Aminophylline shares the actions and uses of other theophylline compounds, over which it has the advantage of greater solubility. It is useful as a peripheral vasodilator and myocardial stimulant for the relief of pulmonary edema or paroxysmal dyspnea of congestive heart failure. Its cardiac effects are more pronounced than those produced by other xanthine derivatives, and in addition to the increase in cardiac output and work of the heart induced by myocardial stimulation, the drug produces a diminution of venous pressure in congestive heart failure.

Aminophylline is also useful by intravenous or intramuscular injection in the control of Cheyne-Stokes respiration and for the treatment of paroxysms of bronchial asthma or status asthmaticus.



It is primarily useful in asthma that is refractory to epinephrine and is safer than epinephrine for paroxysmal dyspnea in which the "bronchial" or "cardiac" nature of the attack has not been determined.

While prompt relief of pain has occasionally been observed to follow the administration of this drug in cardiac infarction, this apparently beneficial effect is rare, and there is always danger that the stimulating action of the drug will harm a heart handicapped by a reduced blood supply. Its prophylactic use to prevent either paroxysmal dyspnea of cardiac origin or the pain of coronary disease is undependable. Evidence is not sufficient to warrant the use of the drug in peripheral vascular disease.

**Dosage.**—For diuresis only, aminophylline may be administered orally (tablets) or rectally (suppositories or enemas) in doses of 0.1 to 0.5 Gm. Rectal forms may also be used to relieve attacks of bronchial asthma, especially in children.

Aminophylline is effective by intravenous or intramuscular injection as a diuretic, cardiac stimulant, for lowering venous pressure, for paroxysmal cardiac dyspnea, Cheyne-Stokes respiration and acute paroxysms of bronchial asthma or status asthmaticus, in doses of 0.25 to 0.5 Gm. The intravenous route is preferred because intramuscular injection may be painful. Subcutaneous injection, even more painful, is not recommended. Intravenous injection should be performed slowly to avoid untoward effects.

Aminophylline is also effective by inhalation as an aerosol in the control of dyspnea of cardiac or asthmatic origin. Its beneficial effects by inhalation for other purposes have not as yet been adequately studied.

#### AMERICAN PHARMACEUTICAL COMPANY, INC.

**Suppositories Aminophylline:** 0.5 Gm. in a water-miscible base.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm. plain and enteric coated.

#### BARRY LABORATORIES, INC.

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

#### ERNST BISCHOFF COMPANY, INC.

**Suppositories Aminophylline:** 0.5 Gm. in a specially prepared fatty alcohol base.

**Tablets Aminophylline:** 0.1 Gm.

U. S. patent 2,586,329.

#### THE BLUE LINE CHEMICAL COMPANY

**Solution Aminophylline:** 10 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.



**THE BOWMAN BROS. DRUG COMPANY**

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter. 10 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm. plain and 0.2 Gm. enteric coated.

**BOYLE & COMPANY**

**Tablets Aminophylline:** 0.1 Gm. plain and 0.2 Gm. plain and enteric coated.

**GEORGE A. BREON & COMPANY**

**Solution Aminophylline:** 10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Solution Aminophylline with Benzyl Alcohol 2%:** 2 cc. ampuls. A solution containing 0.24 Gm. of aminophylline in each cubic centimeter.

**BREWER & COMPANY, INC.**

**Solution Aminophylline:** 10 cc. ampuls and 20 cc. vials. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Solution Aminophylline with Benzyl Alcohol 2%:** 2 cc. ampuls. A solution containing 0.24 Gm. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

**BUFFINGTON'S, INC.**

**Solution Aminophylline:** 2 cc. ampuloids. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

10 cc. and 20 cc. ampuloids. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

**COLE CHEMICAL COMPANY**

**Solution Aminophylline with Benzyl Alcohol 1.5%:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm.

**H. E. DUBIN LABORATORIES, INC.**

**Powder Aminophylline:** 15 Gm., 113 Gm. and 454 Gm. bottles.

**Rectal Suppositories Aminophylline:** 0.36 Gm. and 0.5 Gm.

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.24 Gm. of aminophylline in each cubic centimeter.

10 cc. and 20 cc. ampuls. A solution containing 24 mg. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm. plain and 0.2 Gm. plain and enteric coated.

**PAUL B. ELDER COMPANY**

**Solution Aminophylline:** 10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Solution Aminophylline with Benzyl Alcohol 2%:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm.

**ENDO PRODUCTS, INC.**

**Solution Aminophylline with Benzyl Alcohol 2%:** 2 cc. and 10 cc. ampuls. A solution containing 0.24 Gm. and 24 mg., respectively, of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm.

**CARLO ERBA, INC.**

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.25 mg. of aminophylline in each cubic centimeter.

10 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**ESTRO CHEMICAL COMPANY, INC.**

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**THE EVRON COMPANY, INC.**

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm. plain and 0.2 Gm. enteric coated.

**GOLD LEAF PHARMACAL COMPANY**

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm.

**INGRAM LABORATORIES, INC.**

**Solution Ingraloids Aminophylline:** 2 cc. ampuls. A solution containing 0.12 Gm. or 0.24 Gm. of aminophylline in each cubic centimeter.

10 cc. ampuls. A solution containing 24 mg. or 48 mg. of aminophylline in each cubic centimeter.

20 cc. ampuls. A solution containing 24 mg. of aminophylline in each cubic centimeter.

**KEITH-VICTOR PHARMACAL COMPANY**

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm., uncoated; 0.2 Gm., enteric coated.

**KREMERS-URBAN COMPANY**

Solution Aminophylline: 10 cc. and 20 cc. ampuls. A solution containing 24 mg. of aminophylline in each cubic centimeter.

**LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY**

Solution Aminophylline: 2 cc. and 10 cc. ampuls. A solution containing 0.25 Gm. and 25 mg., respectively, of aminophylline in each cubic centimeter.

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

**LINCOLN LABORATORIES, INC.**

Solution Aminophylline: 2 cc. ampuls. A solution containing 0.24 Gm. of aminophylline in each cubic centimeter.

10 cc. and 20 cc. ampuls. A solution containing 24 mg. of aminophylline in each cubic centimeter.

**MALLARD, INC.**

Tablets Aminophylline: 0.1 Gm.

**PAUL MANEY LABORATORIES, INC.**

Encote Tablets Aminophylline: 0.1 Gm. and 0.2 Gm. enteric coated.

Solution Aminophylline: 2 cc. and 20 cc. ampuls. A solution containing 0.25 Gm. and 25 mg., respectively, of aminophylline in each cubic centimeter.

10 cc. ampuls. A solution containing 24 mg. of aminophylline in each cubic centimeter.

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm.

U. S. patent 2,373,763.

**S. E. MASSENGILL COMPANY**

Tablets Aminophylline: 0.1 Gm. and 0.19 Gm.

**MERCK & COMPANY, INC.**

Powder Aminophylline: 30 Gm., 113 Gm. and 454 Gm. bottles.

**THE WM. S. MERRELL COMPANY**

Solution Aminophylline: 10 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

Solution Aminophylline with Benzyl Alcohol 2%: 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

Tablets Aminophylline: 0.1 Gm.



## MEYER CHEMICAL COMPANY

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm., uncoated; 0.2 Gm., enteric coated.

## E. S. MILLER LABORATORIES, INC.

**Solution Aminophylline:** 10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Solution Aminophylline with Benzyl Alcohol 2%:** 2 cc. ampuls. A solution in 1 per cent ethylenediamine containing 0.25 Gm. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.2 Gm. enteric coated.

**Tablets Theophylline Ethylenediamine:** 0.1 Gm. and 0.2 Gm.

## PHARMEDIC CORPORATION

**Solution Aminophylline:** 2 cc. and 10 cc. ampuls. A solution containing 0.24 Gm. and 24 mg., respectively, of aminophylline in each cubic centimeter.

**Suppositories Aminophylline:** 0.36 Gm.

**Tablets Aminophylline:** 0.1 Gm.

## PHYSICIANS' DRUG &amp; SUPPLY COMPANY

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

**Enerels Aminophylline:** 0.1 Gm. and 0.2 Gm. enteric-coated tablets.

**Powder Aminophylline:** 28.35 Gm. and 113.39 Gm. bottles.

**Solution Aminophylline:** 2 cc. and 10 cc. ampuls. A solution containing 0.25 Gm. and 25 mg., respectively, of aminophylline in each cubic centimeter.

**Suppositories Aminophylline:** 0.5 Gm. in a water-soluble Carbowax base.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

## PROFESSIONAL DRUG SERVICE, INC.

**Tablets Aminophylline:** 0.1 Gm. and 0.2 Gm.

## RAYMER PHARMACAL COMPANY

**Solution Aminophylline:** 10 cc. and 20 cc. ampuls. A solution containing 26 mg. and 24 mg., respectively, of aminophylline in each cubic centimeter.

**Solution Aminophylline with Benzyl Alcohol 2%:** 2 cc. ampuls. A solution containing 0.24 Gm of aminophylline in each cubic centimeter.

**Suppositories Aminophylline:** 0.5 Gm.

**Tablets Aminophylline:** 97 mg. and 0.194 Gm., uncoated and enteric coated.

**REXALL DRUG COMPANY**

**Tablets Aminophylline:** 0.19 Gm.

**WILLIAM H. ROREF, INC.**

**Solution Aminophylline:** 2 and 10 cc. ampuls. A solution containing 0.24 Gm. and 24 mg., respectively, of aminophylline in each cubic centimeter.

**G. D. SEARLE & Co.**

**Powder Aminophyllin:** 28.3 Gm., 113.2 Gm. and 454 Gm. containers for compounding use.

**Solution Aminophyllin:** 10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Solution Aminophyllin with Benzyl Alcohol 2%:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

**Suppositories Aminophyllin:** 0.25 Gm. and 0.5 Gm. Each suppository contains 0.25 Gm. and 0.5 Gm., respectively, of aminophyllin, incorporated into a specially compounded wax base.

**Tablets Aminophyllin:** 0.1 Gm. and 0.2 Gm., uncoated and enteric coated.

**SHERMAN LABORATORIES**

**Solution Aminophylline:** 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

10 cc. ampuls. A solution containing 26 mg. of aminophylline in each cubic centimeter.

**CARROLL DUNHAM SMITH PHARMACAL COMPANY**

**Solution Aminophylline:** 10 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**Tablets Aminophylline:** 0.1 Gm., uncoated; 0.2 Gm., enteric coated.

**SMITH-DORSEY, DIVISION OF THE WANDER COMPANY**

**Tablets Aminophylline:** 0.2 Gm.

**TAYLOR LABORATORIES**

**Tablets Aminophylline:** 0.1 and 0.2 Gm., uncoated; 0.2 Gm. enteric coated.

**TESTAGAR & COMPANY, INC.**

Solution Aminophylline: 10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

Solution Aminophylline with Benzyl Alcohol 2%: 2 cc. ampuls. A solution containing 0.25 Gm. of aminophylline in each cubic centimeter.

**S. J. TUTAG & COMPANY**

Tablets Aminophylline: 0.1 Gm.

**THE VALE CHEMICAL COMPANY, INC.**

Tablets Aminophylline: 0.1 Gm., uncoated; 0.1 Gm. and 0.2 Gm., enteric coated.

**VANPELT & BROWN, INC.**

Tablets Aminophylline: 0.1 Gm.

**THE VITARINE COMPANY, INC.**

Solution Aminophylline: 10 cc. and 20 cc. ampuls. A solution containing 25 mg. of aminophylline in each cubic centimeter.

**WARREN-TEED PRODUCTS COMPANY**

Tablets Aminophylline: 0.1 Gm.

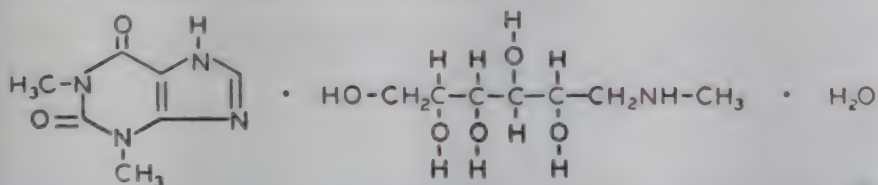
**WYETH LABORATORIES, INC.**

Suppositories Aminophylline: 0.5 Gm. and 0.25 Gm.

**ZEMMER COMPANY, INC.**

Tablets Aminophylline: 0.1 Gm. and 0.2 Gm., uncoated and enteric coated.

**THEOPHYLLINE-METHYLGLUCAMINE.**—Glucophylline (ABBOTT).—An equimolecular mixture of theophylline-U.S.P. ( $C_7H_8N_4O_2 \cdot H_2O$ ) and N-methylglucosamine ( $C_7H_{17}NO_5$ ). Dosage forms of theophylline-methylglucamine contain not less than 95 per cent nor more than 105 per cent of the labeled quantities of theophylline and methylglucamine. The structural formula of theophylline-methylglucamine may be represented as follows:



**Actions and Uses.**—Theophylline-methylglucamine is identical in action and therapeutic purpose to aminophylline-U.S.P. (theophylline ethylenediamine) over which it has no advantage. It is therefore similarly useful orally and by injection to produce the effects of theophylline when a more soluble salt than theophylline and



sodium acetate is needed. It is administered as a peripheral vasodilator and myocardial stimulant for pulmonary edema and paroxysmal dyspnea in congestive heart failure, and for the relief of Cheyne-Stokes respiration. It is also useful in the relief of acute bronchial asthma, particularly in patients who have become unresponsive to epinephrine. As with aminophylline, claims for its use in coronary or peripheral vascular disease and in hypertension are not confirmed by available evidence.

**Dosage.**—Theophylline-methylglucamine represents about 50 per cent of theophylline, as compared to about 78 per cent contained in aminophylline-U.S.P., so that the ratio of dosage to the latter is approximately 3:2. The dosage recommended for theophylline-methylglucamine thus should be about one and one-half times the dose ordinarily prescribed for aminophylline.

The oral dosage is 0.15 to 0.75 Gm. three or four times daily after meals, given for only a few days at a time with intervening rest periods of 1 or 2 days. The intramuscular dosage is 0.75 Gm. in 2 cc.; the intravenous dosage, 0.36 to 0.75 Gm. in 10 to 20 cc. As with aminophylline, intravenous injection should be made slowly to avoid untoward effects.

#### ABBOTT LABORATORIES

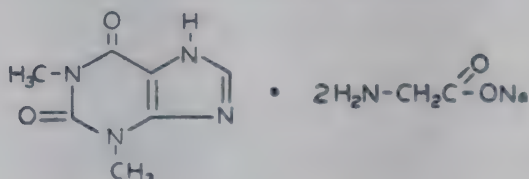
**Solution Glucophylline:** 2 cc. ampuls. A solution containing 0.36 Gm. of theophylline-methylglucamine in each cubic centimeter.

**Suppositories Glucophylline (Rectal):** 0.5 Gm.

**Tablets Glucophylline:** 0.15 Gm. and 0.3 Gm.

U. S. patent 2,161,114. U. S. trademark 334,367.

**THEOPHYLLINE-SODIUM GLYCINATE.**—Cinaphyl (ASCHER).—Dorsaphyllin (SMITH-DORSEY).—Glynazan (FIRST TEXAS CHEMICAL).—Glytheonate (PATCH).—Synophylate (CENTRAL).—Theoglycinate (BRAYTEN).—Theophylline-sodium glycinate contains slightly more than 2 moles of sodium glycinate to 1 mole of theophylline. It contains not less than 49 nor more than 52 per cent theophylline-U.S.P. The structural formula of theophylline-sodium glycinate may be represented as follows:



**Physical Properties.**—Theophylline-sodium glycinate is a white, odorless powder with the characteristic bitter taste of theophylline. It decomposes between 190 and 210°. It is freely soluble in water and is decomposed by acids.

**Actions and Uses.**—Theophylline-sodium glycinate has the typical action of solubilized forms of theophylline such as theophylline sodium acetate and theophylline ethylenediamine (aminophylline),

with the advantage that it is more stable in air and less irritating to the gastric mucosa. It is thus tolerated in larger oral doses than are possible with other theophylline preparations, and it can be administered by mouth in liquid form as well as in tablets not enteric coated. It is incompatible with acidic drugs. Theophylline-sodium glycinate is only slightly less soluble than aminophylline and is also suitable for intravenous injection. It can be administered alone or alternated with penicillin as an aerosol for inhalation in the treatment of severe bronchial asthma. Until more evidence becomes available, theophylline-sodium glycinate should be used only for the purposes recognized for aminophylline. Its value in cardiac conditions other than paroxysmal cardiac dyspnea is not established.

**Dosage.**—Theophylline-sodium glycinate consists of approximately 50 per cent of anhydrous theophylline, whereas aminophylline consists of approximately 80 per cent. The dose of theophylline-sodium glycinate should thus be about one-third more than that of aminophylline.

The oral dose of powder, tablets, elixir or syrup, given every 4 to 6 hours: Adults, 0.3 to 1 Gm.; children over 12 years, 0.15 to 0.4 Gm.; children, 6 to 12 years, 0.1 to 0.2 Gm.; children, 3 to 6 years, 0.13 Gm.; children 1 to 3 years, 0.065 to 0.13 Gm. The powder or tablets are administered preferably with water after meals. Until rectal doses for children are established, suppositories are recommended only for adults. The adult rectal dose is 0.78 Gm. every 4 to 6 hours.

The initial intravenous dose in emergencies is 0.4 Gm. in 10 cc. of distilled water for injection, administered slowly to test its effectiveness and the tolerance of the patient. When necessary, twice this amount (0.8 Gm. in 20 cc.) may be administered slowly and repeated three to four times daily until oral therapy can be instituted or resumed.

Theophylline-sodium glycinate may be administered as an aerosol by nebulization with oxygen of a 5 to 10 per cent solution for inhalation, preferably under a canopy. Nebulization of 2 cc. of such a solution every four hours may be effective in refractory cases of bronchial asthma; very severe dyspnea may require continuous therapy or alternate inhalation of nebulized anti-infective agents such as penicillin.

**B. F. ASCHER & COMPANY, INC.**

**Tablets Cinaphyl:** 0.33 Gm.

**BRAYTEN PHARMACEUTICAL COMPANY**

**Powder Theoglycinate:** Bulk; 113 Gm. bottles, for compounding use.

**Suppositories Theoglycinate:** 0.78 Gm.

**Syrup Theoglycinate:** 240 cc. bottles. A syrup containing 32 mg. of theophylline-sodium glycinate in each cubic centimeter.

**Tablets Theoglycinate:** 0.325 Gm.

U. S. trademark 501,300.

**THE CENTRAL PHARMACAL COMPANY**

**Powder Synophylate:** 113 Gm.

**Solution Synophylate:** 10 cc. and 20 cc. ampuls. A solution containing 40 mg. of theophylline-sodium glycinate in each cubic centimeter.

**Suppositories Synophylate:** 0.78 Gm.

**Syrup Synophylate:** 480 cc. and 3.84 liter bottles. A syrup containing 82 mg. of theophylline-sodium glycinate in each cubic centimeter.

**Tablets Synophylate:** 0.16 Gm. and 0.33 Gm.

**FIRST TEXAS CHEMICAL MANUFACTURING COMPANY**

**Elixir Glynazan:** 473 cc. and 3.78 liter bottles. An elixir containing 70 mg. of theophylline-sodium glycinate in each cubic centimeter.

**Powder Glynazan:** 113 Gm. and 454 Gm. bottles.

**Syrup Glynazan:** 473 cc. and 3.78 liter bottles. A syrup containing 35 mg. of theophylline-sodium glycinate in each cubic centimeter.

**Tablets Glynazan:** 0.324 Gm. and 0.162 Gm.

**THE E. L. PATCH COMPANY**

**Powder Glytheonate:** 113 Gm. and 454 Gm. bottles.

**Suppositories Glytheonate:** 0.78 Gm.

**Syrup Glytheonate:** 473 cc. and 3.78 liter bottles. A syrup containing 65 mg. of theophylline-sodium glycinate in each cubic centimeter.

**Tablets Glytheonate:** 0.324 Gm.

U. S. trademark 507,062.

**SMITH-DORSEY, DIVISION OF THE WANDER COMPANY**

**Suppositories Dorsaphyllin:** 0.78 Gm.

**Elixir Dorsaphyllin:** 473 cc. and 3.78 liter bottles. An elixir containing 32.5 mg. of theophylline-sodium glycinate in each cubic centimeter.

**Tablets Dorsaphyllin:** 0.32 Gm.



## Enzymes

The enzymes presently accepted for inclusion in New and Non-official Remedies have been grouped together in this chapter in the belief that the increasing use of this class of agents will necessitate separate classification.

**HYALURONIDASE.**—**Alidase** (SEARLE).—**Enzodase** (SQUIBB).—**Hyazyme** (ABBOTT).—**Wydase** (WYETH).—Hyaluronidase is an enzyme or enzyme-complex which is capable of hydrolyzing the mucopolysaccharide, hyaluronic acid. It can be isolated from various bacterial cultures or animal tissues. The activity of the enzyme is usually determined either by measuring the reduction in turbidity which hyaluronidase produces when it acts on a substrate containing native hyaluronate and certain proteins, or by measuring the reduction in viscosity which hyaluronidase produces on a buffered solution of sodium or potassium hyaluronate. At present, each manufacturer defines his product in terms of turbidity-reducing units or viscosity units, depending on the system of standardization used. These units are not equivalent since they are measures of different properties of the enzyme.

**Actions and Uses.**—Hyaluronic acid, an essential component of the "ground substance" of tissues, limits the spread of fluids and other extracellular material. Since hyaluronidase softens tissue hyaluronic acid, the enzyme causes injected solutions or local accumulations of fluids (transudates and blood) to spread further and faster than normal and facilitates their absorption.

Hyaluronidase may be used to increase the spread, and consequently the absorption, of hypodermoclysis solutions; to diffuse local anesthetics at the site of injection, particularly in nerve block anesthesia; to increase the diffusion and absorption of other injected materials such as penicillin; and to increase the diffusion and absorption of local accumulations of transudates or blood.

Hyaluronidase also enhances local anesthesia in surgery of the eye. It is useful when administered as a cone injection in glaucoma, since it causes a temporary drop in intra-ocular pressure.

Since it has been shown that hyaluronidase may increase the protective urinary colloids, the agent may be used as an adjunct in the treatment and prevention of urinary calculi.

Hyaluronidase is practically nontoxic, but caution must be used in administering it to patients with infections. The enzyme may cause local infections to spread through the same mechanism by which the spread of injected solutions is facilitated. *Until further evidence is available, hyaluronidase should not be injected into or about an infected area.*

Sensitivity to hyaluronidase occurs infrequently. It can be discovered by testing the skin in the usual manner.

**Dosage.**—Hyaluronidase is supplied in dried form because it deteriorates on standing in solution. The extemporaneously prepared solutions for injection should contain 150 turbidity-reducing units or 500 viscosity units dissolved in 1 cc. of isotonic sodium chloride solution or, with the appropriate amount of that salt, in distilled water. This solution is added to each 1,000 cc. of hypodermoclysis fluid or injected at the site to be employed immediately prior to instituting the clysis. Special care is advisable in pediatric patients to control the speed and total volume of fluid administered to avoid over-hydration; in children less than three years of age the volume of a single clysis should be limited to 200 cc.; in premature infants and during the neonatal period, the daily dosage should not exceed a volume of 25 cc. per kilogram of body weight; the rate of administration should not exceed 2 cc. per minute. In adults the rate and volume of administration should not exceed that employed for intravenous infusion.

The agent also is used for addition to drug preparations or to small amounts of anesthetic solutions for subcutaneous injection. For nerve block or infiltration requiring larger amounts of anesthetic solution, 150 turbidity-reducing units or 500 viscosity units and 0.5 cc. of epinephrine hydrochloride 1:1,000 are added to each 50 cc. of solution and injected intracutaneously, subcutaneously, or intramuscularly.

For local anesthesia of the eye, 150 turbidity-reducing units or 500 viscosity units are dissolved in 1 cc. of a 2 per cent procaine hydrochloride solution (or equivalent amount of other anesthetic to be used) and 0.4 per cent potassium sulfate. For nerve block, 0.4 cc. of this mixture is diluted to 10 cc., and 0.12 cc. (two drops) of epinephrine hydrochloride 1:1,000 is added prior to injection. For cone injection, twice as much epinephrine may be used.

#### ABBOTT LABORATORIES

**Hyazyme:** Vials containing 150 turbidity-reducing units of sterile lyophilized hyaluronidase.

U. S. trademark 564,637.

#### G. D. SEARLE & Co.

**Alidase (Dried):** Ampuls containing 500 viscosity units of powdered hyaluronidase and 9 mg. of sodium chloride.

U. S. trademark 570,583.

#### E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Enzodase Lyophilized:** Vials containing 150 or 1,500 turbidity-reducing units of powdered hyaluronidase. Preserved with 0.02 mg. and 0.2 mg. of thimerosal, respectively.

#### WYETH LABORATORIES, INC.

**Lyophilized Wydase:** Ampuls containing 150 or vials containing



1,500 turbidity-reducing units of powdered hyaluronidase. Preserved with 0.2 mg. of thimerosal.

**Solution Wydase:** 1 cc. and 10 cc. vials. A solution containing 150 turbidity-reducing units of hyaluronidase in each cubic centimeter. Preserved with 0.01 per cent thimerosal. Stabilized with 0.1 per cent disodium ethylenediaminetetraacetic acid and buffered with 0.14 per cent sodium phosphate.

U. S. trademark 542,829.

## Streptodornase

Streptodornase is a desoxyribonuclease, or a specific series of such enzymes, produced by the growth of hemolytic streptococci. Most strains of this organism produce a streptodornase (desoxyribonuclease), but the nature of the streptodornase produced may not be similar in every case. Desoxyribonucleases may also be produced by other micro-organisms, such as pneumococci, and from beef pancreas. The desoxyribonuclease from beef pancreas, as purified by Kunitz, is a single enzyme and can liquefy the fibrils of polymerized desoxyribonucleic acid, but it does not continue the degradation through to purine and pyrimidine compounds which occurs with streptodornase.

Streptodornase acts directly upon a substrate of desoxyribonucleoprotein and desoxyribonucleic acid, which are the chief constituents within the nuclei and constitute 30 to 70 per cent of the sediment of thick purulent exudates. The nucleoprotein is split into free purine bases and pyrimidine nucleosides, thus causing a drop in the viscosity of purulent material. In addition to its depolymerase action, there is a progressive liberation of acid-soluble phosphorus and nitrogen from the substrate, with no increase in uric acid. The enzyme thus produces a striking decrease in degenerated leucocytes and a rapid disappearance of all extracellular desoxyribonucleoprotein. Its action requires the presence of the magnesium ion that is universally present in tissues. It acts only on extracellular nucleoprotein or nuclei of degenerating cells; it does not attack the nuclei or nucleoprotein of living cells and there is no evidence of species specificity. The concentration of streptodornase bears a linear relation to its depolymerase activity, which is highest between pH 7.0 and 8.5 and is optimal at about pH 7.5. Thermal inactivation increases with the temperature, especially above 45°. Streptodornase activity is inhibited by citrate and heparin, but not by other commonly employed drugs which have been tested. Streptodornase is antigenic and capable of stimulating production of antistreptodornase. Its specific antibody, anti-streptodornase, has not been found to interfere significantly with streptodornase activity when the enzyme is used in relatively large amounts.

## Streptokinase

Streptokinase is an extracellular enzyme activator produced by



the growth of various groups of hemolytic streptococci, among which human strains of Lancefield's Group C are a highly potent source. Streptokinase was originally designated as fibrinolysin, but later was renamed because of studies that determined its action was not on fibrin or fibrinogen, but rather that the fibrinolytic activity observed resulted from the activation by streptokinase of a fibrinolytic factor in human serum (euglobulin fraction of plasma). The human serum factor is termed plasminogen (profibrinolysin of Loomis, euglobin factor, lysing factor of Milestone) and, when activated, splits fibrin into polypeptides, causing dissolution of blood clots and fibrinous exudates. It is theorized that streptokinase changes the serum factor plasminogen into an active enzyme plasmin which then catalyzes fibrinolysis. The presence of a spontaneous fibrinolytic enzyme in human blood explains the slow dissolution of sterile blood clots stored for long periods in test tubes and the liquefaction of cadaver blood. Clotting apparently changes plasminogen into plasmin. Although certain nonspecific substances such as chloroform and epinephrine are capable of converting plasminogen to plasmin, streptokinase is unique in its specificity and the rapidity with which it transforms plasminogen to plasmin. Under the influence of plasmin, insoluble fibrin and soluble fibrinogen undergo a mild proteolysis to smaller soluble proteins or large polypeptides with only approximately 10 per cent evolved as nonprotein nitrogen. Streptokinase has maximal activity at a reaction between pH 7.3 and 7.6. At a reaction of pH 5.0 it is inactivated, but can be reactivated if the reaction is adjusted to pH 7.3 to pH 7.6. At a reaction of pH 9.0 or above, streptokinase is irreversibly inactivated.

Streptokinase may also stimulate the production of antistreptokinase, which specifically inhibits the streptokinase transformation of plasminogen to plasmin by streptokinase. Normally, the fibrinolytic action of the latter serum factor is prevented by a serum inhibitor designated antiplasmin. Streptokinase does not affect antiplasmin but by increasing plasmin through its activation of plasminogen, the plasmin/antiplasmin balance is overcome to permit fibrinolysis. The balance between fibrinolysin and antifibrinolysin (plasmin/antiplasmin) is reported to be under control of the pituitary gland through stimulation of adrenal cortical hormones; the tendency toward increased fibrinolysis in shock can be counteracted if sufficient cortical hormones are produced to accelerate the combination of the fibrinolytic enzyme with its inhibitor.

**STREPTOKINASE-STREPTODORNASE.** — **Varidase** (LEDERLE). — Streptokinase-Streptodornase is a mixture composed of enzymes derived from the growth of a strain of *Streptococcus hemolyticus* together with phosphate buffer salts. Streptokinase is a proteolytic enzyme active in the solution of fibrin. Streptodornase is a proteolytic enzyme active in depolymerization of desoxyribonucleic acid, a component of pus. It is assayed by bacteriologic and biologic methods.

**Actions and Uses.**—Streptokinase and streptodornase are proteolytic extracellular enzymes produced by cultural growth of hemo-

lytic streptococci (Lancefield's Group C, human strain H46A). These enzymes are employed together in solution as a purified bacteria-free filtrate which has been frozen and dried. The filtrate is purified and this purification may effect a reduction in the relative amounts of other enzymes produced during the fermentation, such as hyaluronidase and ribonuclease. It may also contain certain enzyme-inhibiting substances whose action is minimized by appropriate dilution. The active enzymes function best in a slightly alkaline solution, thus the filtrate is buffered to maintain a pH of  $\pm 7.5$ .

In addition to their proteolytic activity, streptokinase and streptodornase stimulate two types of nonspecific reaction, a local outpouring of fluid and phagocytes at the site of application and, in certain instances, a foreign protein type of pyrogenic reaction that is attributed to the absorption of cleavage products produced by the enzymes. The latter reaction occurs usually only when the enzymes are injected into a closed space, especially when this is limited and drainage is delayed.

Streptokinase and streptodornase are used to remove clotted blood or fibrinous or purulent accumulations present following trauma or inflammation, thereby facilitating the action of anti-infective forces (humoral and antibiotic) and encouraging normal repair of tissues. The enzymes are clinically established for use as an adjunct in the treatment of hemothorax, hematoma, empyema and chronic suppurations involving draining sinuses, osteomyelitis, infected wounds or ulcers and other common suppurative lesions. As an adjunct to surgical intervention in the care of chronic suppurations, the enzymes may aid in making secondary closure more effective. They should be employed as supplements rather than as substitutes for surgical debridement and drainage. They also may be of value as an aid in the prevention of post-operative adhesions. The enzymes do not act upon fibrous tissues, mucoproteins or collagen; thus, whenever an area of hemorrhage or pyogenic exudate is in a state of organization, their action is less efficacious. They are of no value in the treatment of inflammations unless suppuration is present.

Streptokinase and streptodornase should not be employed in the presence of active hemorrhage or acute cellulitis without suppuration, because they may interfere with clotting or encourage the spread of nonlocalized infections. When bronchopleural fistulas have been present there is danger of reopening, especially with active tuberculosis. With other types of fistulas, the enzymes may be used with proper precautions.

Streptokinase and streptodornase must not be administered intravenously.

**Dosage.**—Streptokinase and streptodornase are applied by injection into cavities and topically by means of wet dressings or added to other materials suitable for keeping the enzymes in close contact with the substrate. The enzymes are used as a solution containing 100,000 Christensen units of streptokinase and at least 25,000 units of streptodornase in not less than 10 cc. of isotonic sodium chloride solution. For a hemothorax or thoracic empyema



an initial dose of 200,000 units of streptokinase and 50,000 units of streptodornase is recommended for injection into one or more sites, as indicated. The most effective final concentration ranges from 100 to 500 units per cubic centimeter of the fluid in situ. For treatment of tuberculous empyema the special procedures reported in the literature should be followed carefully. For exudates within small, enclosed spaces, the size and concentration of the dose should be related to the size of the cavity. In general, this should provide for the increased volume that results from the liquefying action of the enzymes. For example, a suitable initial dose in maxillary sinus empyema would be 10,000 to 15,000 units of streptokinase and 2,500 to 3,750 units of streptodornase in 2 to 3 cc. of solution. For enzymatic debridement, similar concentrations may be applied by means of suitable dressings (this is still under investigation to determine optimal methods). Adequate provision should be made for complete drainage of the liquefied exudate. In a fixed rigid space the dosage interval for repeated injections will range from 30 minutes to 6 hours, depending on the size of the space; in empyemas of the chest, 12 to 24 hours usually is suitable. The amount and character of the fluid aspirated or drained serve as a guide to the number of applications required. This must be evaluated to determine whether the drainage results from increased inflammatory activity or from unresolved exudate requiring further enzyme treatment. Streptokinase usually produces a demonstrable effect within one hour and streptodornase somewhat sooner. Maximal liquefaction is usually obtained within 12 to 24 hours. The action of the enzymes is self-limiting, within 24 to 48 hours, because of the interference of serum inhibitors and because a state of equilibrium is reached between substrates and end products. In addition, the action of streptokinase is limited by the amount of human serum factor present. Since both enzymes are antigenic and stimulate production of antienzymes, these may reduce activity after 2 to 3 weeks unless larger amounts are employed to offset such inhibition. Appropriate precautions are necessary to avoid allergic reaction in sensitive patients.

Solutions deteriorate in potency at room temperatures and may be held for 7 days at 2 to 10° (35.6 to 50° F.). Strict aseptic precautions are essential to avoid contamination.

**LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY**

**Powder Varidase:** 24 cc. vial. A sterile powder containing the equivalent of 100,000 units of streptokinase and 25,000 units of streptodornase. Buffered with sodium phosphates to a pH of 7.5. Preserved with thimerosal 1:10,000.



## Gastro-intestinal Agents

The class of drugs affecting the motor and secretory activities of the gastro-intestinal tract is very large. The present chapter includes only antacids, cholagogues, emollients and laxatives. Certain other drugs that affect the secretions and movements of the gastro-intestinal tract will be found in the chapter on autonomic drugs.

### ANTACIDS

The purpose of antacid therapy is to neutralize effectively the continuously secreted acid gastric juice. Effective neutralization generally is regarded as achieving a pH of 4.0 or 5.0; at this hydrogen ion concentration, the hydrochloric acid and, simultaneously, the peptic activity are practically eliminated. Antacids act locally upon the gastric content; since they do not inhibit the activity of the acid secreting cells, their effects are temporary and disappear when the medication is discontinued.

Aluminum hydroxide is less effective than calcium carbonate in neutralizing gastric acidity in patients with peptic ulcer.

**ALUMINUM HYDROXIDE PREPARATIONS.**—**Alkagel** (LANTEEN).—**Al-U-Creme** (MACALLISTER).—**Amphojel** (WYETH).—**Creamalin** (WINTHROP-STEARN).—Aluminum hydroxide is available commercially as Aluminum Hydroxide Gel-U.S.P. and Dried Aluminum Hydroxide Gel-U.S.P.—“Aluminum Hydroxide Gel is a suspension containing the equivalent of not less than 3.6 per cent and not more than 4.4 per cent of aluminum oxide ( $\text{Al}_2\text{O}_3$ ), in the form of aluminum hydroxide and hydrated oxide.

“Note—Sufficient peppermint oil, glycerine, sucrose, or saccharin may be added to Aluminum Hydroxide Gel for flavoring and other purposes. Sodium benzoate or benzoic acid in an amount not exceeding 0.5 per cent may be added as a preservative.”

“Dried Aluminum Hydroxide Gel yields not less than 50 per cent of aluminum oxide ( $\text{Al}_2\text{O}_3$ ).” *U.S.P.*

**Physical Properties.**—Aluminum hydroxide gel is a white, viscous suspension, translucent in thin layers, from which small amounts of water may separate on standing.

**Actions and Uses.**—Aluminum hydroxide is an effective gastric antacid neutralizing hydrochloric acid of the stomach by chemical reaction. It has none of the principal disadvantages of soluble basic salts: It does not increase the pH of the gastric juice to the point of interference with peptic digestion, does not stimulate a compensatory increase in free gastric acidity and does not produce systemic alkalization. The amphoteric nature of alumi-

num hydroxide is not of clinical significance because it reacts as an acid only in fluids with a pH above 9; such a pH is not encountered in the gastro-intestinal tract. Its so-called buffer action occurs only at a pH of about 4. It is presumed that the acid salt aluminum chloride, which is formed by the reaction of aluminum hydroxide with hydrochloric acid in the stomach, is reconverted to the original compound or other aluminum compounds by reaction with the less acid contents of the small intestine, and that the chloride is reabsorbed.

Its mild astringent and demulcent properties are believed to be of some importance in the local effect on peptic ulcer. Its effectiveness may be further explained by the tendency to increase mucin secretion and the ability to precipitate pepsin in vitro. This action has not been demonstrated in vivo.

Like other aluminum compounds, aluminum hydroxide is not absorbed from the gastro-intestinal tract to any appreciable extent and is therefore nontoxic when administered orally. Because of its astringency, it may cause constipation.

Administration of excessive amounts of aluminum compounds may interfere with the absorption of certain minerals and can produce a phosphorus deficiency. This does not result from ordinary doses employed in indigestion, peptic ulcer and gastric hyperacidity, and the diet employed in these conditions is ordinarily rich in phosphorus. Aluminum hydroxide may possess adsorptive properties, but specific conclusive evidence that acids, toxins, bacteria or gases are adsorbed is lacking. Its reaction with hydrochloric acid is completely accounted for on the basis of simple chemical neutralization.

Aluminum hydroxide is recognized for oral use as an adjunct in the treatment of peptic ulcer (gastric and duodenal) to promote healing, relieve pain and control hemorrhage and for the control of gastric hyperacidity. Its oral or rectal use in the treatment of other gastro-intestinal conditions is not adequately supported by clinical evidence.

**Dosage.**—Aluminum hydroxide is administered orally as aluminum hydroxide gel-U.S.P. in doses of 4 to 8 cc. in one-half glass of water or milk every two or four hours, or one-half to one hour after meals. It may be administered by continuous drip by stomach tube in dilutions of 1 part to 2 or 3 parts of water (25 to 33⅓ per cent aluminum hydroxide gel) at the rate of 15 to 20 drops a minute for a total of approximately 1,500 cc. of diluted suspension per 24 hours.

Tablets of dried aluminum hydroxide gel-U.S.P. may be used when it is difficult or inconvenient for the patient to take the liquid form. A 0.3 Gm. tablet is equivalent in antacid effect to 4 cc. of the suspension.

LANTEEN MEDICAL LABORATORIES, INC.

Tablets Alkagel: 0.32 Gm. and 0.65 Gm.

U. S. trademark 335,060.

**MACALLISTER LABORATORY**

**Al-U-Creme:** 480 cc. and 3.84 liter bottles. A suspension containing 5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide) with saccharin sodium and oil of peppermint as flavoring agents.

**PAUL MANEY LABORATORIES**

**Gel Aluminum Hydroxide:** 480 cc. bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent of aluminum oxide.

**PHYSICIANS' DRUG & SUPPLY COMPANY**

**Tablets Dried Aluminum Hydroxide Gel:** 0.3 and 0.65 Gm.

**THE RESERVE RESEARCH COMPANY**

**Gel Aluminum Hydroxide:** 360 cc. bottles. A suspension containing 5.5 per cent of aluminum hydroxide (equivalent to 3.6 per cent of aluminum oxide) and oil of peppermint, orange and vanilla as flavoring agents.

**Gel Aluminum Hydroxide (Unflavored):** 360 cc. bottles. A suspension containing 5.5 per cent of aluminum hydroxide (equivalent to 3.6 per cent of aluminum oxide).

**WILLIAM H. RORER, INC.**

**Gel Aluminum Hydroxide:** 355 cc. and 3.79 liter bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent of aluminum oxide.

**Tablets Dried Aluminum Hydroxide Gel (Flavored):** 0.3 Gm.

**THE UPJOHN COMPANY**

**Gel Aluminum Hydroxide:** 237 cc. and 3.78 liter bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent of aluminum oxide.

**THE VALE CHEMICAL COMPANY, INC.**

**Tablets Dried Aluminum Hydroxide Gel:** 0.324 Gm.

**VELTEX COMPANY**

**Gel Aluminum Hydroxide:** 480 cc. and 3.84 liter bottles. A suspension containing the equivalent of 3.95 to 4.3 per cent of aluminum oxide with saccharin and oil of peppermint as flavoring agents and sodium benzoate as a preservative.

**THE VITARINE COMPANY, INC.**

**Gel Aluminum Hydroxide:** 236.5 cc., 473 cc. and 3.78 liter containers. A suspension containing aluminum hydroxide equivalent to 4 per cent of aluminum oxide, with soluble saccharin and oil of peppermint as flavoring agents and preserved with sodium benzoate.

**WINTHROP-STEARNs, INC.**

**Creamalin:** 240 cc. and 480 cc. bottles. A suspension containing



5.5 per cent aluminum hydroxide (equivalent to 3.6 per cent aluminum oxide). Oil of peppermint is added as a flavoring agent.

WYETH LABORATORIES, INC.

**Suspension Amphojel (Flavored):** 180 cc. and 360 cc. bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent aluminum oxide, 5 per cent glycerin and not more than 0.5 per cent sodium benzoate. Flavored with oil of peppermint.

**Suspension Amphojel (Unflavored):** 180 cc. and 360 cc. bottles. A suspension containing the equivalent of 3.6 to 4.4 per cent aluminum oxide, 5 per cent glycerin and not more than 0.5 per cent sodium benzoate.

**Tablets Amphojel:** 0.3 Gm. and 0.6 Gm.

U. S. trademark 370,518.

**ALUMINUM PHOSPHATE PREPARATIONS.**—**Phosphaljel (WYETH).**—Aluminum phosphate is available commercially as Aluminum Phosphate Gel-U.S.P.—“Aluminum Phosphate Gel is a water suspension containing not less than 3.8 per cent and not more than 4.5 per cent of aluminum phosphate ( $\text{AlPO}_4$ ).

“Note—Sufficient peppermint oil, glycerin, sucrose, or saccharin may be added to Aluminum Phosphate Gel for flavoring and other purposes. Sodium benzoate or benzoic acid in an amount not exceeding 0.5 per cent may be added as a preservative.” *U.S.P.*

**Physical Properties.**—Aluminum phosphate gel is a white, viscous suspension from which small amounts of water may separate on standing. The pH of aluminum phosphate gel at 25° is between 6.0 and 7.2.

**Actions and Uses.**—Aluminum phosphate has antacid, astringent and demulcent properties analogous to those of aluminum hydroxide but does not interfere with phosphate absorption. Because the acid-combining power of aluminum phosphate is less than one-half that of aluminum hydroxide of the same concentration, it is necessary to prescribe amounts more than twice as great. Indications for the selection of aluminum phosphate include ulcers if a high phosphate diet cannot be continuously maintained or if they are accompanied by a deficiency of pancreatic juice or by diarrhea. Aluminum phosphate gives as good results as aluminum hydroxide in the treatment of peptic ulcers when it is employed in sufficient amounts.

**Dosage.**—During the active stage of the ulcer, 15 to 30 cc. of the suspension, aluminum phosphate gel-U.S.P. alone or with water or milk may be administered every 2 hours. Later the dose may be reduced to 45 cc. four times daily (with or after each meal and at bedtime) or to 30 cc. six times daily (with or after and between meals and at bedtime).

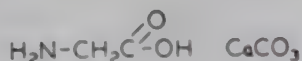
WYETH LABORATORIES, INC.

**Phosphaljel:** 360 cc. bottles. A suspension containing 4 per cent of aluminum phosphate, 1.5 per cent of glycerin, not more than

0.5 per cent of sodium benzoate as a preservative and oil of peppermint as a flavoring agent.

U. S. patent 2,294,889. U. S. trademark 397,011.

**AMINOACETIC ACID AND CALCIUM CARBONATE.**—**Titralac** (SCHENLEY).—Glycine and calcium carbonate.—A mixture containing 30 per cent of aminoacetic acid-N.F. and 70 per cent of calcium carbonate-U.S.P. The formulas of these compounds may be represented as follows:



**Physical Properties.**—Aminoacetic acid and calcium carbonate is a white, odorless, crystalline powder having a slightly sweetish taste. The aminoacetic acid is soluble in water; the calcium carbonate is insoluble.

**Actions and Uses.**—Aminoacetic acid and calcium carbonate, in the above proportions, produce an acid neutralization curve simulating that of whole milk in vitro. The combination is used as a gastric antacid for the control of symptomatic hyperacidity and of peptic ulcer. The rapid buffering action of aminoacetic acid supplements the alkalinizing effect of calcium carbonate. The combination does not produce the acid "rebound" phenomenon nor the systemic alkalosis frequently attributed to the use of alkalies alone. It may be particularly suited for use as a source of calcium in patients unable to take milk, but its buffering action is in no way superior to that which might be achieved with a diet rich in milk and cream. The only claim recognized for the effect of aminoacetic acid is that it has acid buffering action in the mixture.

**Dosage.**—Aminoacetic acid and calcium carbonate is administered orally in doses containing 0.15 Gm. of aminoacetic acid and 0.35 Gm. of calcium carbonate. One such dose provides, within 12 minutes, acid neutralization equivalent to that of 250 cc. of milk. For symptomatic gastric hyperacidity, one or two doses are taken after meals or as needed. As an aid in the management of peptic ulcer, one or two doses are taken at hourly intervals until symptoms are brought under control.

SCHENLEY LABORATORIES, INC.

**Liquid Titralac:** 236 cc. bottles. A suspension containing 60 mg. of aminoacetic acid and 0.14 Gm. of calcium carbonate in each cubic centimeter.

**Powder Titralac:** 113 Gm. jars. Each gram contains 0.3 Gm. of aminoacetic acid and 0.7 Gm. of calcium carbonate.

**Tablets Titralac:** Each tablet contains 0.15 Gm. of aminoacetic acid and 0.35 Gm. of calcium carbonate.

U. S. patent 2,429,596.



**BASIC ALUMINUM CARBONATE.**—**Basaljel (WYETH).**—An aluminum hydroxide-carbonate complex, available only as an aqueous suspension containing the equivalent of 4.9 to 5.3 per cent of aluminum oxide ( $\text{Al}_2\text{O}_3$ .—F.W. 101.94) and not less than 2.4 per cent of carbon dioxide ( $\text{CO}_2$ .—F.W. 44.01). Basic aluminum carbonate suspension is prepared by the interaction of aluminum salts and carbonates.

**Physical Properties.**—Basic aluminum carbonate as a suspension is a white, creamy, thixotropic gel which may separate to some extent on standing. On exposure to atmospheric pressure, the preparation gradually loses carbon dioxide; it must be kept in tightly closed containers. The pH of basic aluminum carbonate suspension is between 6.6 and 7.0.

**Actions and Uses.**—Like aluminum hydroxide, but unlike aluminum phosphate, basic aluminum carbonate combines with the phosphate ion in the intestinal tract to form insoluble aluminum phosphate which is excreted as such in the stool. This diminishes the amount of phosphate available for intestinal resorption, which temporarily lowers the serum inorganic phosphorus and favors more complete tubular resorption by the kidney, thus reducing urinary excretion of phosphate. Basic aluminum carbonate is about one-third more effective than aluminum hydroxide in phosphorus-binding power; this is partly attributed to its greater aluminum content. Therefore, basic aluminum carbonate is primarily useful, in conjunction with a low phosphorus diet, to reduce the concentration and precipitation of urinary phosphate in patients susceptible to the formation of phosphatic calculi of the urinary tract. It may thus be used as an adjunct in the prevention or management of phosphatic stone formation in the kidneys, ureters and bladder. Limitation of phosphorus intake and diversion of phosphate through the intestine by means of basic aluminum carbonate is proposed to replace the use of urine acidifiers and the acid-ash diet for control of the urinary precipitation of phosphate when the latter method is ineffectual because of the presence of ammonia-forming bacterial infection or could lead to acidosis resulting from impairment of renal function.

Basic aluminum carbonate shares the antacid properties of other aluminum compounds used to control gastric hyperacidity and as an adjunct in the treatment of peptic ulcer. Its acid-consuming capacity is greater than that of the upper allowable range of an equivalent weight of aluminum hydroxide.

Basic aluminum carbonate is not contraindicated in the presence of kidney damage or in the presence of an alkaline urine caused by persistent infection. It shares the tendency to produce constipation secondary to the mild astringent action that is characteristic of similar aluminum preparations, but usually this can be easily controlled by the concomitant administration of a mild laxative.

**Dosage.**—Basic aluminum carbonate is administered orally. In the management of phosphatic urinary calculi, the dosage should be regulated according to the urinary phosphorus excretion of the patient. The average initial adult dose is 30 cc. four times daily, preferably taken after meals and at bedtime. In the majority of

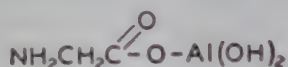


patients, this will reduce urinary phosphate excretion within a few days to 0.2 Gm. or less per 24 hours. The urinary phosphate should be determined at least once a month, and the patient should be placed on a diet designed to provide a daily mineral intake of 1.3 Gm. of phosphorus, 0.7 Gm. of calcium and 13 Gm. of nitrogen, and to furnish about 2,500 calories. Such a diet can be followed for an indefinite period by the average ambulant patient. The average adult antacid dose is 4 to 8 cc., repeated as necessary to control gastric hyperacidity.

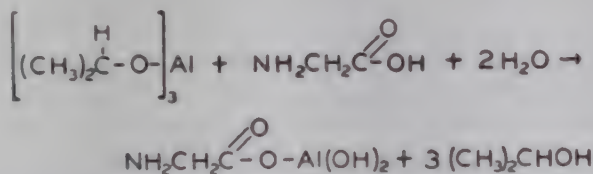
#### WYETH LABORATORIES, INC.

**Suspension Basaljel:** 360 cc. bottles. A flavored aqueous suspension containing the equivalent of 4.9 to 5.3 per cent of aluminum oxide and not less than 2.4 per cent of carbon dioxide.

**DIHYDROXY ALUMINUM AMINOACETATE.**—Alglyn (BRAYTEN).—Aspogen (EATON).—Alzinox (PATCH).—Doraxamin (SMITH-DORSEY).—Robalate (ROBINS).—A basic aluminum salt of aminoacetic acid containing small amounts of aluminum hydroxide and aminoacetic acid. The structural formula of dihydroxy aluminum aminoacetate may be represented as follows:



Dihydroxy aluminum aminoacetate is prepared by the reaction of aluminum isopropoxide with aminoacetic acid according to the following reaction:



The precipitated dihydroxy aluminum aminoacetate is filtered with suction, washed with isopropyl alcohol and dried at a temperature not exceeding 71°. The aluminum isopropoxide is prepared by the reaction of aluminum in shreds or strips with anhydrous isopropyl alcohol, catalyzed by 0.03 per cent mercuric chloride, followed by distillation under vacuum.

**Physical Properties.**—Dihydroxy aluminum aminoacetate is a white, odorless powder with a faintly sweet taste. It is insoluble in water and organic solvents, but dissolves in dilute mineral acids and solutions of fixed alkalis to yield cloudy solutions which clarify on heating.

**Actions and Uses.**—Dihydroxy aluminum aminoacetate acts as a gastric antacid when taken orally and is thus useful for the control of hyperacidity in the management of peptic ulcer. It shares the properties of the aluminum hydroxide gel preparations and has no important advantages over them. Its buffer action is not

significantly more prompt, greater or more prolonged than that of the liquid preparations of aluminum hydroxide gel when compared on the basis of equivalent aluminum content. Compared with dried aluminum hydroxide gel-U.S.P., it possesses only slightly more prompt buffering action and shares with that preparation the convenience of being used in tablet form. Because it contains from 50 to 60 per cent less aluminum than the aluminum hydroxide preparations, the formation of astringent aluminum chloride in the intestine is theoretically reduced. This is claimed to result in less constipating action. The clinical significance of differences between dihydroxy aluminum aminoacetate and preparations of aluminum hydroxide is open to question, and claims that it is generally superior to aluminum hydroxide preparations are disallowed until more clinical evidence is available. Prompt disintegration in the stomach of dihydroxy aluminum aminoacetate tablets swallowed whole offers only limited advantage since preparations of dried aluminum hydroxide gel may be readily broken up prior to administration if necessary.

**Dosage.**—Dihydroxy aluminum aminoacetate is administered orally: 0.5 to 1 Gm. after meals and at bedtime or as otherwise required to control hyperacidity. As with other internally administered aluminum compounds, constipation may occur from prolonged administration.

**BRAYTEN PHARMACEUTICAL COMPANY**

**Powder Alglyn:** Bulk; for manufacturing use.

**Tablets Alglyn:** 0.5 Gm.

U. S. patent 2,480,743. U. S. trademark 420,509.

**EATON LABORATORIES, INC.**

**Tablets Aspogen:** 0.5 Gm.

U. S. trademark 505,100

**THE E. L. PATCH COMPANY**

**Magma Alzinox:** 250 cc. bottles. A suspension containing 0.1 Gm. of dihydroxy aluminum aminoacetate in each cubic centimeter. Preserved with 0.1 per cent of sodium benzoate.

U. S. patent 2,480,743.

**Tablets Alzinox:** 0.5 Gm.

**A. H. ROBINS COMPANY, INC.**

**Tablets Robalate:** 0.5 Gm.

U. S. trademark 544,956.

**SMITH-DORSEY, DIVISION OF THE WANDER COMPANY**

**Gel Doraxamin:** 473 cc. bottles. A gel containing 0.1 Gm. of dihydroxy aluminum aminoacetate in each cubic centimeter. Preserved with 0.015 per cent of butyl *p*-hydroxybenzoate.

**Tablets Doraxamin:** 0.5 Gm.

**ALMAGUCIN.**—Mucotin (HARROWER).—An antacid mixture of gastric mucin, dried aluminum hydroxide gel-U.S.P. ( $\text{Al}_2\text{O}_3 \cdot x\text{H}_2\text{O}$ ), and magnesium trisilicate-U.S.P. ( $2\text{MgO} \cdot 3\text{SiO}_2 \cdot x\text{H}_2\text{O}$ ), containing the labeled amounts of these ingredients.

**Actions and Uses.**—This mixture of histamine-free gastric mucin, aluminum hydroxide and magnesium trisilicate is an effective combination for oral administration in the control of symptomatic gastric hyperacidity and as an adjunct in the treatment of peptic ulcer. Gastroscopic studies indicate that the mucin-antacid combination may coat the ulcer crater and may remain in the stomach for over an hour after instillation. However, the coating effect ascribed to this preparation requires further confirmation; if it occurs, its therapeutic value remains to be established. Antacid effect is secured by the aluminum hydroxide and magnesium trisilicate.

**Dosage.**—There is as yet no definite evidence by which to determine the optimum proportions of the antacids to be used in the mixture, but best results are obtained with preparations containing approximately 10 per cent of gastric mucin. A ratio of 1:1.5:2.75 for gastric mucin-aluminum hydroxide-magnesium trisilicate produces good results. A tablet preparation of these proportions, containing 0.16 Gm. gastric mucin, 0.25 Gm. dried aluminum hydroxide gel and 0.45 Gm. magnesium trisilicate, is recommended in doses of two tablets every two hours. The tablets should be well chewed and no fluids taken during the following half hour.

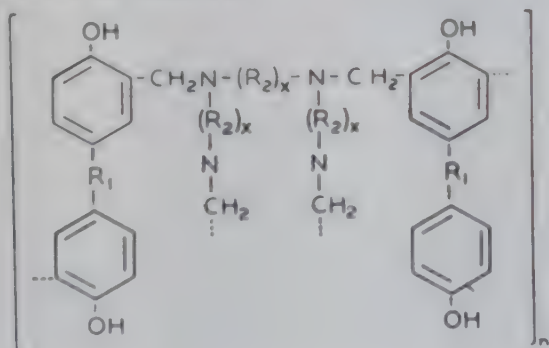
HARROWER LABORATORY, INC.

**Liquid Mucotin:** 355 cc. bottles. A flavored suspension containing 40 mg. of gastric mucin, 62 mg. of aluminum hydroxide gel and 0.11 Gm. of magnesium trisilicate in each cubic centimeter.

**Tablets Mucotin:** Each tablet contains gastric mucin 0.16 Gm., dried aluminum hydroxide gel-U.S.P. 0.25 Gm. and magnesium trisilicate-U.S.P. 0.45 Gm. with excipients and flavoring oils.

U. S. patent 2,472,476, applied for, Lutheran Univ. Assoc., Valparaiso University. U. S. trademark 519,949.

**POLYAMINE-METHYLENE RESIN.**—Exorbin (AYERST).—Resinat (NATIONAL DRUG).—A polyethylene polyamine methylene substituted resin of diphenylol dimethylmethane and formaldehyde in basic form. The structural formula of polyamine-methylene resin may be represented as follows:





**Physical Properties.**—Polyamine-methylene resin is a light amber, granular, freely flowing powder without appreciable odor. It is insoluble in dilute acids and alkalis, alcohol, ether and water; however, a small amount of colored material is extracted by aqueous systems.

**Actions and Uses.**—Polyamine-methylene resin is a synthetic acid-binding resin capable of withdrawing acids from solution by molecular absorption. This property has been utilized clinically by administering the resin orally as a gastric antacid for the control of symptoms in simple hyperacidity and in peptic ulcer. The antacid effects apparently result from temporary binding in the stomach of gastric hydrochloric acid and pepsin which are later released in the intestine. The resin itself is then eliminated unchanged from the gastro-intestinal tract without any permanent ionic disturbance of the body fluids. Like other antacids, this resin should be regarded as only an adjunct in the treatment of peptic ulcer; it is not recommended in the treatment of gastritis, "heart-burn" or dyspepsia, which may or may not be associated with increased gastric acidity. Recommendations for its use in simple gastric hyperacidity should not imply that it is of value in all diseases in which this condition exists, unless it can be demonstrated that the symptoms are directly related to the hyperchlorhydria.

Polyamine-methylene resin is essentially nontoxic, but large doses may induce nausea or vomiting unless the taste of the resin is suitably masked.

**Dosage.**—Polyamine-methylene resin is administered orally in the form of powder, capsules or tablets. For the relief of symptoms in acute or chronic peptic ulcer, 0.5 to 1 Gm. every 2 hours is recommended, but larger doses may be necessary in some cases. The dosage required depends partially on the amount and frequency of food consumption. This drug should not be employed as a substitute for the customary dietary restrictions in the treatment of peptic ulcer. For administration as a powder, the resin should be quickly stirred in water, milk or other liquid, but it is probably more palatable in the form of capsules or tablets.

AYERST LABORATORIES, INC.

Tablets Exorbin: 0.25 Gm.

U. S. trademark 530,289.

NATIONAL DRUG COMPANY

Capsules Resinat: 0.25 Gm.

Tablets Resinat: 0.5 Gm.

U. S. patent 2,581,035. U. S. trademark 519,752.

## EMOLLIENTS

**GASTRIC MUCIN.**—The fraction precipitated by approximately 60 per cent alcohol from the supernatant liquid after pepsin-hydrochloric acid digestion of hog stomach linings.

**Physical Properties.**—Gastric mucin is a white to yellow powder

or brownish yellow granules. It has a slightly salty taste and characteristic odor indicative of peptones. Both forms yield a viscous gray, opalescent solution when triturated with water.

**Actions and Uses.**—Gastric mucin is used in the treatment of peptic ulcer. Its therapeutic action is considered to be that of protecting and lubricating the mucosa of the stomach and duodenum. Currently available preparations of gastric mucin do not effectively neutralize gastric acidity in man.

**Dosage.**—The average dose is 2.5 Gm., which can be given at 2-hour intervals.

#### WILSON LABORATORIES

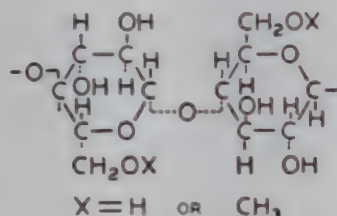
Granules Gastric Mucin: 226.8 Gm. and 453.6 Gm. packages.

Powder Gastric Mucin: 453.6 Gm. packages.

## LAXATIVES

**METHYLCELLULOSE-N.F.**—Cellothyl (WARNER-CHILCOTT).—Syn-celose (BLUE LINE).—"Methylcellulose is a methyl ether of cellulose containing not less than 26 per cent and not more than 33 per cent of methoxyl groups ( $-\text{OCH}_3$ )."—*N.F.*

The structural formula of methylcellulose may be represented as follows:



**Physical Properties.**—Methylcellulose is a grayish white, fibrous powder; its aqueous suspensions are neutral to litmus paper. It swells in water and produces a clear to opalescent, viscous, colloidal solution. It is insoluble in alcohol, in ether and in chloroform.

**Actions and Uses.**—Methylcellulose is used in chronic constipation. This state usually results from a combination of nervous tension, improper dietary and fluid intake, failure to heed the call to stool, lack of exercise and the abuse of laxatives. Hence the administration of drugs should be only an adjunct to re-educative measures.

Taken with water, the drug forms a colloidal solution in the upper alimentary tract; this solution loses water in the colon to produce a gel which increases the bulk and softness of the stool. In the course of a few days the patient may be able to resume more normal bowel habits, and the initial dose should be reduced to a level adequate for maintenance of good function. The drug is customarily continued for weeks or months, usually at reduced dosage. The gelatinous nature of the colonic contents, which results

from the use of methylcellulose, may be helpful in patients with colostomies.

**Dosage.**—For adults, 1 to 1.5 Gm. in the form of tablets or granules, with water, two to four times daily; later 1.5 Gm. once or twice daily may be sufficient.

For infants and children, 0.5 Gm. as granules, sprinkled on food or stirred in water, two to three times daily.

#### THE BLUE LINE CHEMICAL COMPANY

Tablets Syncelose: 0.5 Gm.

WARNER-CHILCOTT LABORATORIES, DIVISION OF WARNER-HUDNUT, INC.

Granules Cellothyl: 25 and 100 Gm. bottles.

Tablets Cellothyl: 0.5 Gm.

U. S. trademark 428,768.

**PLANTAGO OVATA COATING.**—Konsyl (BURTON, PARSONS).—A preparation consisting principally of the separated outer mucilaginous layers of *Plantago ovata* seeds (blond psyllium).

**Physical Properties.**—*Plantago ovata* coating is a cream-colored to brown, granular powder, which is practically odorless and tasteless.

**Actions and Uses.**—*Plantago ovata* coating may be used in cases of simple constipation due to lack of sufficient bulk in the stool. It produces no cathartic action and is, therefore, mainly useful as an aid in chronic constipation of functional or nervous origin.

**Dosage.**—5 to 10 Gm. three times daily, usually before meals, in a glass of water or milk, is sufficient to promote evacuation of the bowel in most cases. It is important that the mixture be taken before it thickens.

#### BURTON, PARSONS & COMPANY

Powder Konsyl: 180 Gm. and 360 Gm. cans.

U. S. patent 1,975,731. U. S. trademark 313,620.

**PSYLLIUM HYDROPHILIC MUCILLOID WITH DEXTROSE.**—Metamucil (SEARLE).—A mixture containing about 50 per cent of the powdered mucilaginous portion (outer epidermis) of blond psyllium seeds (*Plantago ovata*-Forsk) and about 50 per cent of powdered anhydrous dextrose, with 0.2 per cent sodium bicarbonate, 0.25 per cent monobasic potassium phosphate, 0.33 per cent citric acid and 0.04 per cent benzyl benzoate.

**Physical Properties.**—Psyllium hydrophilic mucilloid with dextrose is a white to cream colored, slightly granular powder with little or no odor and a slightly acid taste. A uniform suspension is formed when 10 Gm. of the powder is stirred rapidly into 250 ml. of water. As the hydration and swelling of the mucilaginous portion progresses, the mixture assumes a soft gelatinous consistency.

**Actions and Uses.**—Psyllium hydrophilic mucilloid with dextrose is intended as an adjunct in the treatment of constipation. It encourages elimination by the formation of a soft, plastic, water-



retaining gelatinous residue in the lower bowel. The mucilloid also has a demulcent effect in the presence of inflamed mucosa. Psyllium hydrophilic mucilloid with dextrose has been mixed with barium sulfate to obtain more uniform dispersion of the barium for x-ray visualization.

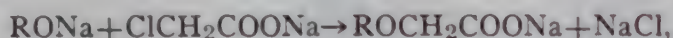
**Dosage.**—Four to 7 Gm. one to three times daily, each dose thoroughly stirred in a glass of cool water or other liquid and followed by an additional glass of liquid. Children receive proportionately less according to weight and age. It is important that adequate fluids be ingested to assure a soft bulk. Psyllium hydrophilic mucilloid with dextrose should not be used carelessly as dependency may ensue.

G. D. SEARLE & Co.

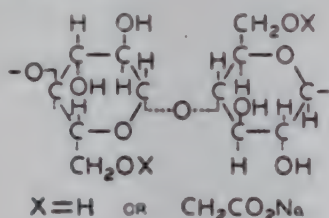
**Metamucil:** 113 Gm., 227 Gm. and 454 Gm. containers.

U. S. patent 2,095,259 and 2,132,484. U. S. trademark 317,704.

**SODIUM CARBOXYMETHYLCELLULOSE.**—**Thylose Sodium (JACKSON-MITCHELL).**—Sodium carboxymethylcellulose is prepared by the reaction of alkali cellulose with sodium monochloroacetate according to the following equation:



where R represents the cellulose structure. The reaction conditions are chosen to give about 0.8 of a sodium carboxymethyl group ( $\text{NaO}_2\text{C}-\text{CH}_2-$ ) for each anhydroglucose unit in the cellulose molecule. The structural formula of sodium carboxymethylcellulose may be represented as follows:



**Physical Properties.**—Sodium carboxymethylcellulose is a white to light buff, odorless, hygroscopic powder. On heating, it browns between 226 and 228° and chars between 252 and 253°. A 1 per cent solution has a viscosity between 1,300 and 2,200 centipoises and a pH between 6.5 and 8.0.

**Actions and Uses.**—Sodium carboxymethylcellulose is a synthetic hydrophilic colloid gum. It is similar to methylcellulose in forming a soft bulk in the bowel after oral ingestion. Sodium carboxymethylcellulose differs in its action from methylcellulose in that it is insoluble in gastric juices. It is a satisfactory and desirable adjunct to re-education in the treatment of chronic constipation.

**Dosage.**—The usual dose is 1.5 Gm. three times daily with meals, accompanied by one or two glasses of water.

JACKSON-MITCHELL PHARMACEUTICALS, INC.

**Tablets Thylose Sodium:** 0.5 Gm.

## Hormones and Synthetic Substitutes

This chapter includes substances that are internally secreted by particular organs whence they are carried by blood or lymph to other organs for the control of growth or activity. Such substances are called endocrine secretions or hormones. Included here also are a number of artificial substances that are important in therapeutics because their actions so closely resemble those of the natural substances.

### ADRENALS

#### Adrenal Cortex

The cortex of the adrenal gland is essential for life. Adrenalectomized animals die in a few days. Effects of acute adrenal insufficiency, in disease or after experimental procedures in animals, include blood concentration, low blood pressure, gastro-intestinal disturbances, asthenia, subnormal temperature and low basal metabolic rate. There also may be loss of sodium and retention of potassium in most species, loss of carbohydrate reserves with hypoglycemia and retention of nitrogenous products in the blood. Injections of suitable extracts of adrenal cortex which contain little or no epinephrine may restore even moribund animals to apparently vigorous health for as long as the injections are continued, especially if sodium chloride and water are administered concurrently.

**Adrenal Cortical Extracts.**—Extracts of the adrenal cortex contain several potent substances which influence electrolyte, water or carbohydrate metabolism to various degrees. These substances tend to regulate the number of circulating eosinophils and the activity of thymus and lymphoid tissue. They also exert influence over skin pigmentation in human beings. However, as demonstrated on small animals, no one of these substances and no synthetic substance possesses all the effects of a potent cortical extract.

Adrenal cortex extracts have been assayed in many ways. There are advantages to each method, but the maintenance of life in the adrenalectomized animal is the most significant measure of activity for such extracts. For N. N. R. descriptions, the Council has recognized the assay method devised by Pfiffner, Swingle and Vars (*J. Biol. Chem.* 104:701, 1934) and the slight modification used by Cartland and Kuizenga (*Am. J. Physiol.* 117:678, 1936). For uni-



formity of potency, these methods express the activity of adrenal cortex preparations in terms of dog units based on their ability to maintain the life of adrenalectomized dogs. An alternate assay method using adrenalectomized rats according to the procedure of Cartland and Kuizenga (*Am. J. Physiol.* 117:678, 1936) may also be employed and the results transposed into dog units, provided sufficient data are presented that such a comparison of assays is justified. No preparation of adrenal cortex extract will be accepted for inclusion in *New and Nonofficial Remedies* that does not have a minimum of 50 dog units or 2.5 rat units per 1 cc. of extract when assayed by the Cartland and Kuizenga method.

**The Adrenal Steroids.**—There have been isolated from the cortex crystalline compounds which are capable of maintaining the life of adrenalectomized animals and restoring toward normal the disturbed metabolic conditions induced by adrenal insufficiency. These compounds are steroids.

The chemical structure of the cortical steroids is closely related to that of the sex hormones; in fact, some of the cortical steroids have estrogenic or androgenic properties and in certain abnormal conditions of the cortex large amounts of androgens, and occasionally estrogens, may be recovered in the urine. On the other hand, the sex hormone progesterone has life-maintaining properties in adrenal insufficiency in small animals, while other sex hormones such as estrone and testosterone are capable of inducing slight electrolyte changes similar to those produced by cortical steroids. The steroids of the adrenal cortex may be divided structurally into the 11-desoxysteroids and the 11- and 11, 17-oxysteroids. Desoxycorticosterone belongs to the first class and, as its name indicates, lacks an oxygen atom at position 11 in the steroid nucleus. Its activity is limited chiefly to the electrolyte and water regulating function (mineralo-corticoid or sodium retaining hormone). The addition of oxygen at position 11 apparently is accompanied by potentiality for regulation of gluconeogenesis (gluco-corticoids), but the most potent compounds, cortisone and hydrocortisone, possess an oxygen atom also at position 17 (11, 17-oxysteroids). These three compounds, desoxycorticosterone, cortisone and hydrocortisone, have been prepared synthetically and are used clinically.

The adrenal cortex also plays a role in gluconeogenesis and therefore enters into the regulation of carbohydrate, fat and protein metabolism. Cortisone and hydrocortisone possess these powers to the greatest degree among isolated adrenal steroids. From in vivo studies it appears that hydrocortisone (compound F) may be the principal glucogenic steroid secreted by the adrenal cortex. In addition to their metabolic regulatory role, hydrocortisone and cortisone also regulate electrolyte exchange in the kidney tubules, but to a lesser degree than desoxycorticosterone.

With the availability of cortisone and hydrocortisone, extracts of the adrenal cortex, which were formerly the only preparations available, are required less frequently. Their principal indication is in the treatment of acute adrenal insufficiency.



**ADRENAL CORTEX EXTRACT.**—An extract of adrenal glands of domesticated animals which man uses for food, containing the cortical steroids essential for the maintenance of life in adrenalectomized animals. The extract is prepared according to the method of Cartland and Kuizenga (*J. Biol. Chem.* 116:57, 1936). Frozen adrenal glands are extracted with acetone and the extract is purified by selective precipitation and extraction technics. Only traces of epinephrine are present.

**Physical Properties.**—Adrenal cortex extract is a water-soluble extract obtained following extraction of the adrenal glands with fat solvents. Each cubic centimeter is obtained from not less than 40 Gm. of gland and contains not less than 50 dog units. The activity of the extract is relatively stable, especially if maintained at refrigerator temperature. Alcohol 10 per cent is used as a preservative.

**Actions and Uses.**—Although the extract is active by mouth, this method of administration is not to be depended on for therapeutic purposes. The usual methods of administration are subcutaneous, intramuscular or intravenous injection. The extract is of value in the treatment of Addison's disease and other types of adrenal insufficiency, and in surgical procedures involving the adrenal cortex when prophylactic measures are needed to prevent the development of temporary adrenal insufficiency. Aqueous adrenal cortical extracts may be of value in the treatment of acute stress situations such as severe overwhelming infections (Waterhouse-Friderichsen syndrome) and burns. There is no conclusive proof of the value of the extract in borderline cases of adrenal insufficiency.

**Dosage.**—The amount required for therapeutic purposes varies widely according to the degree of cortical insufficiency, the condition of the patient, the presence of infection, crises and other complications. The clinical response of the patient should govern the dosage. As much as 2,500 to 5,000 dog units (50 dog units = 2.5 rat units = 0.1 mg. of 17-hydroxycorticosterone) within a few hours may be required for a patient in a severe crisis, while from 500 dog units daily may be sufficient substitution in some cases of Addison's disease. Large amounts of sodium chloride or other sodium salts are of definite value in supplementing adrenal cortex extracts.

#### ARMOUR LABORATORIES

**Solution Adrenal Cortex Extract:** 10 cc. vials. Each cubic centimeter contains 3 mg. of extractive solids, with a biologic activity equivalent to 0.1 mg. of 17-hydroxycorticosterone. The solids are mainly a mixture of the physiologically active cortical steroids. It is physiologically standardized on adrenalectomized rats by using 17-hydroxycorticosterone and determining liver-glycogen deposition. Preserved with 10 per cent alcohol.

U. S. patent 2,096,342.

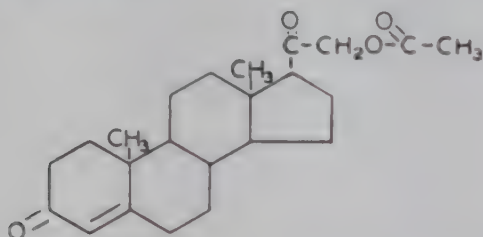
#### THE UPJOHN COMPANY

**Solution Adrenal Cortex Extract:** 10 cc. and 50 cc. vials. 50 dog units per cubic centimeter. Each cubic centimeter contains not more than 3 mg. of gland extractives, having a potency equivalent

to 50 dog units when assayed by the Cartland-Kuizenga method, in physiologic solution of sodium chloride. Preserved with 10 per cent alcohol.

U. S. patent 2,096,342.

**DESOXYCORTICOSTERONE ACETATE-U.S.P. — Doca Acetate (ORGANON).** — 17-( $\beta$ )-[1-Keto-2-acetoxyethyl]- $\Delta^4$ -androstene-3-one.—The structural formula of desoxycorticosterone acetate may be represented as follows:



**Physical Properties.**—Desoxycorticosterone acetate is a white, crystalline powder. It is odorless and is stable in air. It is practically insoluble in water. It is sparingly soluble in alcohol, acetone and in dioxane. It is slightly soluble in vegetable oils.

**Actions and Uses.**—Desoxycorticosterone has been isolated from the adrenal cortex in small amounts and is prepared synthetically as the acetate. Desoxycorticosterone acetate is highly selective in its biologic activity. It has no demonstrable direct effect on protein or carbohydrate metabolism in man and little if any in experimental animals. It has no effect on estrogenic or androgenic activity or on pigmentation. Its known activity is limited to the metabolism of sodium, potassium and water and is mediated through its action on the renal mechanism. It causes an increase in retention of the sodium ion and water and an increase in the excretion of potassium, presumably by modification of reabsorption of these substances by the renal tubules. Therapeutic dosages, in patients with adrenal insufficiency, restore the serum sodium and potassium and the plasma volume to normal levels. The drug also elevates the blood pressure. Secondary to the increase in blood volume, there results an increase in cardiac output with a decrease in nitrogen retention, increase in the absorption of fat and glucose from the intestine and increase in strength as well as appetite.

Desoxycorticosterone acetate, despite its limited range of physiologic activity, may be used in the management of adrenal insufficiency, both in maintenance and in the treatment of crises. Many patients with chronic adrenal insufficiency are enabled to resume normal activity by the administration of desoxycorticosterone acetate and sodium chloride alone. However, most clinicians prefer the use of cortisone or hydrocortisone with supplemental sodium chloride for the treatment of Addison's disease; desoxycorticosterone in small doses also may be used as a supplement. In the treatment of patients with acute adrenal insufficiency, aqueous adrenal cortical extracts, the gluco-corticoids and desoxycorticosterone are all employed.



Significant toxicity results from excessive amounts of desoxycorticosterone acetate. The most frequent signs are edema, pulmonary congestion, cardiac dilatation and failure. Arterial hypertension develops in about 30 per cent of patients with chronic adrenal insufficiency after treatment for several months or years. This may require a cautious reduction in the dosage of the steroid or salt or both. Occasionally toxicity due to decrease in serum potassium concentration is associated with sudden attacks of weakness and characteristic changes in the electrocardiogram.

**Dosage.**—The dosage of desoxycorticosterone acetate required for maintenance varies from 1 to 7 mg. daily. It depends primarily on individual variation and on the amount of sodium salts in the diet; i.e., the higher the salt intake the lower the requirement of the adrenal steroid. Experience indicates that most patients require about 3 mg. daily when taking 3 to 6 Gm. of sodium chloride in addition to that contained in the normal diet.

In the management of acute adrenal crises, 10 to 15 mg. may be required twice a day for 1 or 2 days in conjunction with liberal quantities of whole adrenal cortical extract or cortisone and with one or two daily infusions of 1,500 cc. of 5 per cent dextrose in isotonic sodium chloride solution. Transfusion of whole blood or plasma may also be indicated to combat shock.

Desoxycorticosterone acetate is insoluble in water and usually administered in oil by subcutaneous or intramuscular injection. After the maintenance dose has been carefully determined, pellets may be implanted subcutaneously to avoid repeated injections. A pellet of 0.12 Gm. is absorbed slowly, exerting an effect approximately equivalent to that of daily injections of 0.5 mg. Desoxycorticosterone pellets are usually effective for 9 to 15 months. Symptoms of adrenal insufficiency begin to recur when the pellets have been completely absorbed. Crumbling of pellets may result in increased absorption and evidence of overdosage.

ORGANON, INC.

**Solution Doca Acetate in Oil:** 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 5 mg. of desoxycorticosterone acetate in each cubic centimeter.

U. S. patent 2,312,481. U. S. trademark 372,214.

### Glucocorticoids

The two principal adrenal steroids concerned in gluconeogenesis and members of the 11, 17-oxysteroid series are hydrocortisone and cortisone. Their activity is essentially similar, although hydrocortisone probably is more active, weight for weight, and is less irritating to the synovial membranes when injected into joint spaces. The carbohydrate-regulating hormones of the adrenal cortex have been called glucocorticoids, and for convenience this term will be utilized to designate cortisone and hydrocortisone in the following discussion, as they are the sole members of the group available commercially.



When injected into adrenalectomized animals, the gluco-corticoids maintain life and resistance to various forms of stress ordinarily lethal to the unprotected adrenalectomized animal. The gluco-corticoids affect fat, protein and carbohydrate metabolism promoting gluconeogenesis, hyperglycemia, glycosuria and negative nitrogen balance. They inhibit the activity of the lymphatic system, producing lymphopenia and reduction in the size of enlarged lymph nodes. In comparison with desoxycorticosterone, which is an adrenal corticoid of the 11-desoxy series, cortisone and hydrocortisone induce only mild sodium retention and potassium excretion, but large doses given over a period of several days may alter the electrolyte balance profoundly. Hydrocortisone and cortisone increase urinary excretion of creatine and uric acid but do not change creatinine excretion. The effect on renal excretion of calcium and phosphorus is variable.

The gluco-corticoids also affect the reticuloendothelial system, causing increased production of serum globulin and reversal of the normal albumin globulin ratio. In some instances the gluco-corticoids exert an effect upon blood coagulation. Decrease in prothrombin time has been noted, and there may be an increased tendency to develop thrombo-embolic phenomena.

Therapeutic dosages of the gluco-corticoids in the human being depress the function of the adrenal cortex and inhibit the production of corticotropin by the pituitary. Continued use of the hormones causes atrophy of the thymus and varying degrees of atrophy of the adrenal cortex. On sudden cessation of therapy, the adrenal cortex usually recovers from the partial atrophy and depression of function induced by the gluco-corticoids, but the danger of permanent adrenal atrophy must always be considered. The hormones therefore should be withdrawn gradually rather than abruptly, particularly if they have been given in large doses for a few days, and the patient observed for signs of deficient adrenocortical function. Clinically, this depression of cortical function may be manifested by lassitude, weakness and lethargy. Surgical or medical emergencies during this period of reduced adrenal function may require prompt re-employment of the gluco-corticoids (or corticotropin, if the adrenal cortex is capable of response) to enable the patient to survive the stress. Because of the effects on electrolyte balance, laboratory and metabolic studies should be performed before and during protracted therapy with cortisone and hydrocortisone. Measurement of fluid intake and output and daily weighing may give early indication of fluid retention. It may be wise to maintain the patient on an intake of less than 1 Gm. of sodium per day with supplemental potassium.

Significant increase in blood pressure may result from therapeutic doses of gluco-corticoids when antecedent vascular or renal damage is present or when retention of sodium and water develops.

When the gluco-corticoids are administered to patients over extended periods, they may cause widespread physiologic and metabolic effects resembling those encountered in Cushing's syndrome. Although not all of the signs have been induced in any one patient, one or more of the following have been observed: rounded,

moonlike facial contours, hirsutism, acne, cervicothoracic hump, muscular weakness, hypertension, osteoporosis, edema, amenorrhea, cutaneous striae, impairment of glucose tolerance, negative nitrogen balance, increased corticosteroid excretion, hypochloremic-hypopotassemic alkalosis and mental disturbance. The thin skin, ecchymoses and polycythemia of Cushing's syndrome so far have not been induced by therapy.

The negative nitrogen balance induced by high-dosage glucocorticoid therapy may delay bone and wound healing.

The gluco-corticoids also may reactivate latent tuberculosis, and higher doses of antibiotics may be required to control co-existent bacterial infections than ordinarily would be necessary. Recurrence and activation of peptic ulcer has been reported during gluco-corticoid therapy.

Cortisone and hydrocortisone have various effects on the nervous system. Usually, the patient experiences a feeling of well-being and euphoria. In some instances psychoses have developed; both manic and depressive states have been reported. Alterations in electroencephalographic patterns have been noted. There is evidence which suggests that they possess analgesic effect or increase the patient's capacity to bear pain.

The gluco-corticoids are indicated chiefly for substitution therapy in frank adrenal insufficiency, such as may be encountered in Addison's disease, panhypopituitarism and after adrenalectomy, and in certain acute conditions where the period of treatment is not long enough to incur the metabolic effects of protracted therapy, i.e., to prevent shock in patients with adrenocortical tumors who are to undergo surgery of the adrenal glands. Saline suspension parenterally, implanted pellets and oral tablets of the hormones or their esters have been employed successfully, both alone and conjointly with desoxycorticosterone acetate and sodium chloride in the treatment of Addison's disease. The gluco-corticoids may be used concomitantly with colchicine to abort acute attacks of gouty arthritis. Colchicine should be continued after cessation of corticoid therapy to prevent the exacerbation of symptoms which usually follows withdrawal of the hormone. The gluco-corticoids also have been effective in allergic states, such as serum sickness, status asthmaticus and intractable hay fever, and in exfoliative dermatitis. They have been employed both parenterally and locally to control inflammations of the eye, including allergic blepharitis, purulent conjunctivitis, corneal inflammations, anterior and posterior uveitis, iritis, acute choroiditis, sympathetic ophthalmia and retrolental fibroplasia.

Although the gluco-corticoids have been used most extensively in the so-called collagen group of diseases—rheumatoid arthritis, disseminated lupus erythematosus, periarteritis nodosa, dermatomyositis and scleroderma, their effects in these diseases in most instances obtain only during therapy. The mechanism of action is obscure but appears to include a peripheral effect, possibly on "reactivity" or permeability of mesenchymal tissues. Inhibition of the hyaluronidase system and changes in permeability of cell membranes apparently are involved also. When the hormones are



withdrawn, the mesenchymal tissue once more is free to react to the stimulus of the diseases. Thus, cortisone and hydrocortisone as a rule are only palliative in these conditions, and therapy must be maintained for such long periods that undesired metabolic effects may be produced. The onset of undesired effects is a function of the time-dosage relationship; therefore, minimal dosage schedules should be employed.

These hormones induce prompt recession of acute symptoms and signs of acute rheumatoid arthritis, including local redness, swelling and tenderness. After 1 to 2 weeks of treatment, the sedimentation rate usually falls to nearly normal levels and rheumatic nodules regress. However, histologic examination of synovial tissue after several months of therapy has continued to disclose evidence of active rheumatoid arthritis. Following the withdrawal of the hormones, symptoms generally reappear within a short period, rarely longer than a few weeks. Continuation of therapy, even on reduced dosage schedules, may lead to the development of a state resembling Cushing's syndrome. The period of remission obtained by use of these hormones should be employed to begin active physiotherapeutic management of the patient. The acetate esters of cortisone and hydrocortisone may be injected into affected intra-articular spaces for local relief of pain and stiffness in both rheumatoid arthritis and osteoarthritis. Hydrocortisone acetate apparently produces a more prolonged and intense local effect with less irritation than does cortisone acetate.

Acute rheumatic fever has shown encouraging response to glucocorticoid therapy, especially in cases of short duration. Although the end results in the development of subsequent rheumatic valvular disease have not been evaluated, the fever, toxicity and arthralgia respond well to administration of the hormone, although the relief of acute symptoms is no more prompt than with adequate doses of acetylsalicylic acid. The gluco-corticoids must be used with caution in acute rheumatic fever because the tendency to sodium and water retention may induce or aggravate cardiac failure before the hormone's beneficial results are manifested.

Cortisone and hydrocortisone have been lifesaving in fulminating acute disseminated lupus erythematosus and in pemphigus, producing remissions of several months' duration. If renal or cardiac involvement exists, it is wise to guard against the possibility of congestive cardiac failure resulting from sodium and water retention induced by the hormones. Relapse invariably follows cessation of therapy and may be controlled with increasing difficulty by reinstitution of treatment. Neoplastic diseases of the lymphatic system, such as lymphosarcoma, lymphatic leukemia and Hodgkin's disease, show temporary response to gluco-corticoid therapy in some cases, but acute monocytic leukemia and chronic myelogenous leukemia appear to respond unfavorably.

The gluco-corticoids may be employed for relief of symptoms in nonsuppurative thyroiditis, acute Bell's palsy and the allergic manifestations of trichinosis. When other measures fail in the treatment of ulcerative colitis, they also may be used if the potential danger of hemorrhage and perforation is borne in mind.

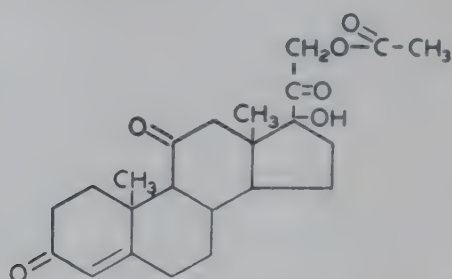


Cortisone and hydrocortisone are such potent hormonal agents that it is advisable to perform laboratory studies periodically as a safeguard against the danger of electrolyte imbalance.

The gluco-corticoids are active by oral, parenteral or topical application. The ratio of oral to parenteral dosage is approximately 1:1. The oral route elicits more rapid but less sustained response and therefore requires repeated administration of the hormones at 6-hour to 8-hour intervals.

The hormones are contraindicated in long-term treatment of any condition complicated by hypertension, diabetes mellitus, congestive heart failure, mental disturbances, chronic nephritis and active or questionably healed tuberculosis. In large dosage they may mask the onset of an acute condition requiring surgery or reactivation of a latent chronic infection. There is evidence to suggest that the gluco-corticoids reduce the resistance of the host to certain infectious processes, such as tuberculosis and some virus diseases. They also have been reported to cause rapid spread of metastatic carcinoma.

**CORTISONE ACETATE.**—Cortogen Acetate (SCHERING).—Cortone Acetate (SHARP & DOHME).—11-Dehydro-17-hydroxycorticosterone-21-acetate.—The structural formula for cortisone acetate may be represented as follows:



**Physical Properties.**—Cortisone acetate is a white, odorless powder. It melts with decomposition between 242 and 248°. It is practically insoluble in water, slightly soluble in ether and alcohol and freely soluble in chloroform.

**Actions and Uses.**—See the general statement on gluco-corticoids.

Cortisone acetate may be used for the control of systemic diseases by parenteral administration of the suspension or by oral ingestion of the tablets. For ophthalmic use, local instillation or injection of suspensions of varying concentrations or application of an ointment have proved effective.

**Dosage.**—Dosage schedules vary with the patient and disease. For optimum response in severe disorders, as much as 0.3 Gm. may be administered the first day, followed by 0.2 Gm. the second day and then 0.1 Gm. daily. Injections of the parenteral solution should be made deep into the gluteal muscles. The daily dose should be divided into three or four equal parts for oral administration. Dosage should be reduced gradually to the minimum regimen which

produces the desired response. To avoid undesirable side effects, courses of treatment should not exceed 6 weeks and should be separated by rest periods of 2 or 3 weeks.

In Addison's disease cortisone acetate may be employed in doses of 5 mg. to 20 mg. daily, either alone or combined with desoxycorticosterone and sodium chloride.

#### SCHERING CORPORATION

**Ophthalmic Suspension Cortogen Acetate:** 5 cc. dropper bottles. A buffered suspension containing 5 or 25 mg. of cortisone acetate in each cubic centimeter. Preserved with benzalkonium chloride 1:5,000.

**Suspension Cortogen Acetate:** 10 cc. vials. A suspension containing 25 mg. of cortisone acetate in each cubic centimeter. Preserved with thimerosal 1:10,000.

**Tablets Cortogen Acetate:** 5 and 25 mg.

U. S. trademark 548,401.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Ophthalmic Ointment Cortone Acetate:** 3.5 Gm. tubes. An ointment containing 15 mg. of cortisone acetate in each gram.

**Ophthalmic Suspension Cortone Acetate 0.5%:** 5 cc. dropper bottles. An isotonic, buffered solution containing 5 mg. of cortisone acetate in each gram. Preserved with 0.02 per cent benzalkonium chloride.

**Ophthalmic Suspension Cortone Acetate 2.5%:** 5 cc. dropper bottles. An isotonic, buffered solution containing 25 mg. of cortisone acetate in each gram. Preserved with 0.02 per cent benzalkonium chloride.

**Suspension Cortone Acetate:** 10 cc. vials. A suspension containing 50 mg. of cortisone acetate in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

**Suspension Cortone Acetate with Benzyl Alcohol 0.9%:** 20 cc. vials. A saline suspension containing 25 mg. of cortisone acetate in each cubic centimeter.

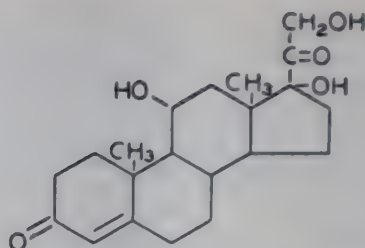
**Tablets Cortone Acetate:** 5 mg. and 25 mg.

#### THE UPJOHN COMPANY

**Suspension Cortisone Acetate with Benzyl Alcohol 1.5%:** 20 cc. vials. An isotonic saline suspension containing 25 mg. of cortisone acetate in each cubic centimeter.

**Tablets Cortisone Acetate:** 5, 10 and 25 mg.

**HYDROCORTISONE.—Cortef (UPJOHN).—Hydrocortone (SHARP & DOHME).—17-Hydroxycorticosterone.**—The structural formula of hydrocortisone may be represented as follows:



**Physical Properties.**—Hydrocortisone is a white, odorless powder which melts between 215 and 220° (with decomposition). It is freely soluble in dioxan and in methanol and very slightly soluble in ether and in water. The approximate amounts which dissolve in the following solvents to form 100 ml. of solution are: 1.8 Gm. in alcohol and 0.4 Gm. in chloroform.

**Actions and Uses.**—See the general statement on gluco-corticoids.

The physiologic and therapeutic effects of hydrocortisone are qualitatively similar to those of cortisone. Comparative clinical studies in patients with rheumatoid arthritis tend to indicate that hydrocortisone is therapeutically effective in smaller doses than cortisone; however, it has not been demonstrated that the incidence of undesirable metabolic or hormonal effects is minimized by the use of hydrocortisone as compared with cortisone.

Hydrocortisone is absorbed readily following oral administration; the effects of oral medication are manifest in 3 to 10 hours and persist about 12 to 14 hours. Its onset and duration of anti-rheumatic action seems comparable with that of cortisone.

**Dosage.**—Hydrocortisone is administered orally. Daily observation is essential to determine individual response and to establish maintenance dosage. Routine determinations of blood pressure and body weight, as well as a urinalysis, electrocardiogram and complete blood count, are essential. Occasionally, such special studies as blood sugar, carbon dioxide combining power and blood electrolytes are advisable. The dosage should be adjusted to the minimum amount which will provide relief adequate for rehabilitation; this adjustment may minimize or avoid hypercortisonism. Studies thus far indicate that the clinically effective oral dosage ratio of hydrocortisone to cortisone is approximately 1:1.6. For rheumatoid arthritis, the initial average adult daily dosage is 80 mg. given in divided doses, two to four times a day, until the desired effect is obtained (not over 2 weeks); the dosage is then reduced by steps of not more than 10 mg. to the minimum effective maintenance level. Withdrawal of treatment should be accomplished by similar gradual reduction. Variations in the daily maintenance dosage should be adjusted to meet the natural fluctuations of the disease, and occasionally therapy should be withdrawn long enough to determine whether remission has occurred. In other diseases, a dose of 20 mg. of hydrocortisone is recommended whenever a 25 mg. dose of cortisone would be indicated. Other dosage also may be estimated on the basis of this same ratio.

The appearance of exaggerated hormonal effects may require



withdrawal of therapy. Surgical candidates should not have the drug withdrawn, for increased dosage may be required. With prolonged therapy, restriction of sodium and administration of potassium chloride may be necessary to maintain electrolyte balance. Temporarily, the cautious use of diuretics may be indicated, but these may provoke a further dangerous loss of potassium. In patients with diabetes mellitus, insulin requirements may be increased. Activity should be restricted in cardiovascular disease.

Continued supervision of patients is essential after discontinuation of therapy because the drug may continue to act for some time after the last dose. A temporary hypoadrenal state, manifested by weakness and hypoglycemia, may occur after abrupt withdrawal, but return of adrenal function may be expected within 2 weeks.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

Tablets Hydrocortone: 5, 10 and 20 mg.

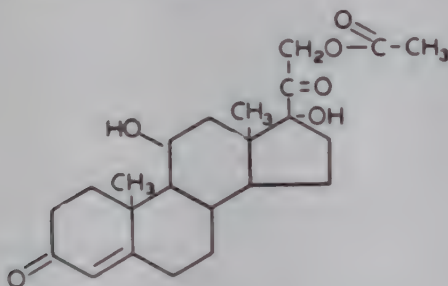
U. S. trademark 536,020.

THE UPJOHN COMPANY

Tablets Cortef: 10 mg.

U. S. trademark 583,191.

**HYDROCORTISONE ACETATE.**—Cortef Acetate (UPJOHN).—Hydrocortone Acetate (SHARP & DOHME).—17-Hydroxycorticosterone-21-acetate.—The structural formula of hydrocortisone acetate may be represented as follows:



**Physical Properties.**—Hydrocortisone acetate is a white, odorless solid. It melts between 218 and 223° (with decomposition). It is very slightly soluble in ether and practically insoluble in water. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 0.45 Gm. in alcohol and 0.73 Gm. in chloroform.

**Actions and Uses.**—See the general statement on gluco-corticoids. When injected systemically, hydrocortisone acetate is capable of producing the same side effects as cortisone acetate. However, when injected intra-articularly or into bursae, systemic side effects have not been observed.

Hydrocortisone acetate is useful for topical application in the form of a 1 or 2.5 per cent ointment for the local management of

allergic dermatoses, such as contact dermatitis and atopic dermatitis (including allergic eczema, disseminated neurodermatitis and eczematoid dermatitis), seborrheic dermatitis and lichenified pruritis. Topical therapy is not recommended for use in such severe systemic diseases as pemphigus and discoid lupus erythematosus, and it is possible that systemic hormone treatment may be required in the management of moderately severe skin conditions. Although local irritation or sensitization to hydrocortisone has not been reported, patients should be observed carefully for possible untoward effects of long-term topical therapy. Topical application should not be made to infected areas.

Hydrocortisone acetate is useful for ophthalmic application as a 0.5 or 2.5 per cent suspension and as a 1.5 per cent ointment in the treatment of nonspecific superficial and deep keratitis, acne rosacea keratitis, herpes zoster ophthalmicus, phlyctenular keratoconjunctivitis, allergic conjunctivitis, chronic and mild acute iritis, recurrent marginal ulceration and secondary glaucoma from anterior uveal inflammation. Topical application principally affects the anterior segment of the eye and has less influence upon deeper structures. Hereditary and degenerative eye diseases in general do not respond to treatment with hydrocortisone acetate.

**Dosage.**—For intra-articular or intrabursal injection the amount to be injected and the interval between injections varies with the degree of inflammation, the size of the involved joint and the individual response of the patient. Small joints or bursae usually require 5 to 10 mg. Larger joints or bursae require 15 to 37.5 mg., repeated when symptoms recur.

For topical application, an ointment containing either 1 or 2.5 per cent is rubbed gently into the involved areas of the skin following thorough cleansing with soap or a similar detergent to reduce the possibility of infection and of the continuing presence of the primary irritant in the skin. The 1 per cent concentration should be used for less severe or more recent skin lesions, whereas the 2.5 per cent may be employed for more severe or long-standing lesions which are responsive to topical medication. The treatment for severe lesions may be reduced to 1 per cent strength or the therapy for milder lesions increased to 2.5 per cent as may be necessary.

For ophthalmic application, a suspension containing 0.5 or 2.5 per cent of the drug is instilled into the conjunctival sac in a dosage of 1 or 2 drops every hour during the day and every 2 hours during the night for the first 2 days. If a favorable response is observed, the dosage then can be reduced to 1 drop every 4 hours and later to three or four times daily. When an eye pad is required, a 1.5 per cent ointment may be preferred to a suspension, applying the ointment three or four times daily; or the ointment may be applied at bedtime in place of a suspension, to avoid disturbing the patient's sleep. Duration of therapy varies with the type of lesion. Ophthalmic application may be employed freely as required because the patient need not be observed for systemic reactions during local treatment. Systemic administration may be required for therapy of deep ocular structures.



SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Ointment Hydrocortone Acetate:** 5 Gm. tubes. An ointment containing either 10 mg. or 25 mg. of hydrocortisone acetate in each gram.

**Ophthalmic Ointment Hydrocortone Acetate:** 3.5 Gm. tubes. An ointment containing 15 mg. of hydrocortisone acetate in each gram.

**Ophthalmic Suspension Hydrocortone Acetate:** 5 cc. dropper bottles. A suspension containing either 5 or 25 mg. of hydrocortisone acetate in each cubic centimeter. Preserved with 0.5 per cent benzyl alcohol and 0.02 per cent benzalkonium chloride.

**Suspension Hydrocortone Acetate:** 5 cc. vials. A saline suspension containing 25 mg. of hydrocortisone acetate in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

THE UPJOHN COMPANY

**Ointment Cortef Acetate:** 5 Gm. tubes. An ointment containing 10 or 25 mg. of hydrocortisone acetate in each gram.

U. S. trademark 583,191.

## OVARIES

Sex hormones, as a rule, are closely related in chemical structure to each other and to the steroids of the adrenal cortex. They also possess physiologic properties in common. For instance, certain androgens possess progestational qualities while progesterone is said to have a slight androgenic activity in laboratory animals. The steroids of the adrenal cortex may account for the virilism, pseudo-puberty or occasional feminism seen in patients with adrenal cortical tumors.

The ovaries produce internal secretions necessary for the proper functioning of the uterus, in particular, for the cyclic growth processes of the endometrium and the development of the decidua; in addition these internal secretions determine cyclic changes in the vagina and cervix and influence the growth of the mammary gland. Hormones given off by the anterior pituitary regulate the growth of the follicles, ovulation and formation of corpus luteum.

During the growth of the ovarian follicles induced by the follicle-stimulating hormone of the anterior pituitary, an estrogenic hormone secreted by the follicles (probably from the cells of the theca interna), evokes certain changes in the accessory organs. The vaginal mucosa thickens and the cells undergo a more intense cornification; the myometrium hypertrophies, while the endometrium rapidly becomes proliferated. At this time the duct system of the breast develops. After ovulation there is a release of the luteinizing hormone of the pituitary, and the collapsed follicle is transformed into a corpus luteum which secretes progesterone. In the human the corpus luteum elaborates estrogenic hormone as well. The progestational hormone induces in the endometrium secretory changes



preparatory to nidation; it also stimulates growth of the alveolar breast tissue. Menstruation occurs when the corpus luteum suddenly ceases to produce progesterone. Estrogen is also low at this time. The intrinsic factors which cause extravasation of blood and tissue fragmentation at the end of the cycle are not yet clear, but involve spasm of the spiral arteries of the endometrium with ischemia, endometrial necrosis and subsequent venous bleeding.

**Estrogen.**—The injection of potent estrogenic substances in castrate animals will induce in the accessory sex organs changes typical of estrus. Long-continued injections, however, induce hypertrophic, and then frequently metaplastic changes in the uterus, cervix and breast. Clinical endometrial hyperplasia, chronic cystic mastitis and fibromyomas may be due to long-continued estrogen secretion by the ovary.

Estrogenic substance is also responsible for the contractility of the uterus and the sensitivity of the myometrium to oxytocic agents. The smooth muscle of the human Fallopian tube is also responsive to estrogenic substance.

The curve of excretion of estrogenic substances in normally menstruating women varies extremely from day to day. In general, however, there is at least one sudden peak at the height of follicular activity during ovulation. Excretion curves in ovarian disorders have not been adequately studied because of technical difficulties in assays. Several methods for the chemical assay of estrogens have been recently introduced. During pregnancy large amounts of estrogens are excreted in the urine in the form of water-soluble conjugate. In pregnant women these are preponderantly in the form of glucuronides, and in pregnant mares in the form of sulfates. Hydrolysis of the urine, either by acid or by putrefaction, converts the conjugated estrogens into their free forms, which are more active physiologically.

Estrogenic substances occur widely in nature, in plants as well as in animals. Estrone (ketohydroxyestrin) and estriol (trihydroxyestrin) are extracted from urine or placentas of humans during pregnancy while several estrogens, including estrone, equilin and hippulin, are obtained from the urine of pregnant mares. Sow's ovaries contain both estrone and estradiol (dihydroxyestrin), but not in sufficient quantities to make them a commercially worthwhile source. Estradiol exists in two stereoisomeric forms—alpha and beta. Originally, the active estrogen was thought to be  $\alpha$ -estradiol, the trans form; however, more recent analyses have demonstrated that it is estradiol-17 $\beta$ , the cis form. Therefore, the substance that was originally called  $\alpha$ -estradiol is in reality estradiol-17 $\beta$ . Since estrogens are rapidly destroyed in the animal body, estrogen compounds which are absorbed slowly from the site of injection may be more efficient. Fatty acid esters of the estrogens (benzoate, acetate, propionate, palmitate) have therefore been prepared for this purpose.

Estrogens are used either orally, intravaginally or by hypodermic injection of a solution in oil or a colloidal suspension in an aqueous solvent. Estrone and estradiol lose considerable activity when taken

orally. When estrone is administered in the form of its sulfate, it retains a greater amount of its potency. Several estrogenic compounds have been prepared which lose relatively little potency when administered orally. Since these are highly active, even when given once daily, they are to be preferred except when oral administration is contraindicated.

Preparations extracted from the urine of pregnant women or pregnant mares may contain crystalline or amorphous estrogenic material. The estrogenic activity of such extracts is due almost entirely to estrone. Synthetic estrogens, which vary in efficiency and severity of side effects, are also available. Physiologic difference between these compounds and the natural steroids has not been demonstrated.

There has been an enormous amount of clinical research with estrogenic substances. Definite and reliable results have been obtained in only a few conditions.

Estrogenic substances are used in a variety of conditions associated with deficiency of estrogens. These include symptoms of the menopause syndrome—natural or induced, senile vaginitis, kraurosis vulvae and pruritus vulvae. Some authorities suggest that estrogens may be given to control vasomotor symptoms of the menopause in doses sufficiently small not to produce endometrial or vaginal epithelial changes. A related use is in the treatment of hypogenitalism in the female; however the use of estrogen in such conditions substitutes for ovarian function but does not stimulate it. Estrogens have been used in attempts to inhibit production of gonadotropic hormone by the anterior pituitary. This requires very large doses. Large doses of estrogen probably do not inhibit lactation immediately postpartum but estrogenic therapy is helpful in relieving the engorgement of breasts especially when lactation is to be suppressed. According to some investigators, estrogenic therapy does not clearly improve the results obtained with the usual measures, dehydration and breast feeding, and may be complicated by postpartum bleeding and a high rate of recurrence of engorgement.

It is possible to interrupt the prolonged or excessive flowing of many women with "functional bleeding" by brief courses of intensive estrogenic therapy. This is considered safe practice only when the interval of freedom from bleeding is used to eliminate local pelvic lesions as the cause of the flowing. The subsequent administration of sequences of estrogenic substances and progesterone to reestablish cycles of flowing is a possible method of alleviating a condition which is widely believed to result from the deficiency of one or both ovarian hormones, but their value for this purpose must be regarded as incompletely established.

Estrogens cause undesirable uterine and vaginal growth and proliferation and frequently withdrawal endometrial bleeding. Since the advent of effective antibiotics, the use of estrogens is no longer indicated in the treatment of gonorrheal vaginitis in children.

Estrogenic materials act together with, or as a substitute for, castration in the palliation of the local discomforts from prostatic



carcinoma and its metastases. The action is apparently not curative but may persist for a number of months.

Estrogens are carcinogenic when administered experimentally to animals which have an inherited sensitivity to the development of mammary carcinoma. Many clinicians believe that estrogens are therefore contraindicated in the treatment of women who have a familial or personal history of mammary or genital malignancy. However, estrogens may be used in treatment of inoperable breast carcinoma.

Some estrogenic substances, notably diethylstilbestrol, ethinyl estradiol, dienestrol, estradiol dipropionate and conjugated estrogenic substances, have been found to exert, under certain conditions, a palliative effect on mammary cancer. Estrogens should never be given to a woman with breast cancer if she is less than 5 years past the menopause or if her disease is amenable to surgery or roentgen therapy.

Estrogens may produce subjective relief of symptoms, and temporary objective improvement particularly of lung and skin metastases. In some patients, however, acceleration of the disease may occur and should this be observed, therapy should be discontinued immediately. Estrogens can cause salt retention and edema which may be dangerous. Such reactions should be combatted by a low salt diet and ammonium chloride or mercurial diuretics; if these methods are ineffective, therapy should be discontinued. Occasionally uterine bleeding may occur, particularly on cessation of therapy. This is usually not serious but patients should be examined carefully to rule out concomitant uterine tumors, which are known to occur not infrequently in older patients with mammary cancer.

**Progesterone.**—The hormone of the corpus luteum induces secretory changes of the endometrium, stimulates growth of the mammary alveolar tissue and relaxes the uterine smooth muscle. It is essential for nidation of the ovum and maintenance of pregnancy. During gestation the ovary elaborates progesterone only through the third month, after which the placenta is responsible for its elaboration. Progesterone is excreted in the form of pregnandiol glucuronide and is found in the urine in pregnancy and during the corpus luteum phase of the normal cycle. Studies on habitual abortion have revealed that pregnandiol excreted in the urine may be abnormally low at about the hundredth day of gestation, indicating an insufficiency of progesterone. Daily administration of 10 to 50 mg. of progesterone sometimes brings the pregnandiol level to normal, but it has not been uniformly efficacious.

Crystalline ethisterone (anhydrohydroxyprogesterone) has progestational activity when administered orally.

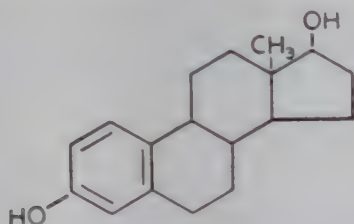
Commercial preparations of progesterone are either extracts of animal ovaries, or the pure compound prepared synthetically. At one time there was considerable enthusiasm over the therapeutic use of such preparations in dysmenorrhea, menorrhagia and habitual abortion, but satisfactory evidence is inadequate to warrant dependence on progesterone.



## Steroid Estrogens

### Parent Estrogens

**ESTRADIOL-U.S.P.—Ovocycin (CIBA).—Alpha-estradiol.—3,17-Dihydroxy- $\Delta$ -1,3,5-estratriene.**—The structural formula of estradiol may be represented as follows:



**Physical Properties.**—Estradiol occurs as white or slightly yellow, small crystals or as a crystalline powder. It is odorless and is stable in air. It is almost insoluble in water; soluble in alcohol, acetone, dioxane and in solutions of fixed alkali hydroxides and sparingly soluble in vegetable oils.

**Actions and Uses.**—Estradiol is considered to be the form of the estrogenic hormone produced by the human ovary and is one of the more potent of the known compounds having estrogenic activity. It therefore shares the actions and uses of other estrogens and is subject to the same contraindications. (Also see the general statement on ovaries and the subsection on estrogen.)

Estradiol is available as the pure crystalline compound, but it is mainly useful when administered orally or topically as an adjunct to parenteral therapy with the esterified compounds of estradiol or other injectable estrogens because it is subject to rapid destruction on injection. It also loses some activity when administered orally.

The use of the ointment for inunction in mammary hypoplasia is of negligible value and offers no advantage over systemic therapy.

**Dosage.**—Estradiol is administered orally in the form of tablets or topically for local treatment of the vagina in the form of suppositories. Dosage is prescribed on the basis of weight rather than on the basis of the unit systems which are sometimes used for impure estrogens or mixtures of various estrogenic substances.

For initial therapy of the menopausal syndrome, 0.5 mg. three times daily usually produces a prompt response; for maintenance, from 0.1 to 0.2 mg. three times daily may be sufficient. When greater response is desired, parenteral therapy with injectable compounds may be used to start treatment, followed by oral maintenance therapy with estradiol alone. (See the monograph on estradiol benzoate.)

For the local treatment in the vagina, a suppository containing 0.4 mg. inserted at bedtime is recommended for adults, in conjunction with systemic therapy. Smaller amounts were formerly used

for local treatment of gonorrheal vaginitis in children, but this method has been abandoned since the advent of penicillin.

**BIORGANIC LABORATORIES, INC.**

**Powder Estradiol:** Bulk; 1 Gm., 5 Gm. and 10 Gm. containers for compounding use.

**CHICAGO PHARMACAL COMPANY**

**Solution Estradiol in Oil:** 1 cc. ampuls and 30 cc. vials. A solution in sesame oil containing 0.14 and 0.28 mg. in each cubic centimeter.

10 cc. vials. A solution in sesame oil containing 0.28 mg. of estradiol in each cubic centimeter. Preserved with 0.5 per cent benzyl alcohol.

**Suspension Estradiol with Benzyl Alcohol 4%:** 30 cc. vials. A suspension containing 0.14 and 0.28 mg. in each cubic centimeter.

1 cc. ampuls. A microsuspension containing 0.14 mg. of estradiol in each cubic centimeter.

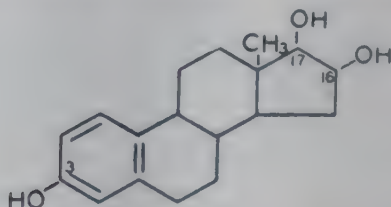
1 cc. ampuls and 10 cc. vials. A microsuspension containing 0.28 mg. of estradiol in each cubic centimeter.

**CIBA PHARMACEUTICAL PRODUCTS, INC.**

**Tablets Ovocilin:** 0.1 mg., 0.2 mg. and 0.5 mg.

U. S. patent 2,096,744. U. S. trademark 362,717.

**ESTRIOL.**—Theelol.—3,16,17-Trihydroxy- $\Delta$ -1,3,5-estratriene.—A crystalline estrogenic steroid isolated from the urine of pregnancy. The structural formula of estriol may be represented as follows:



**Physical Properties.**—Estriol is a white, odorless, microcrystalline powder which exhibits a reddish fluorescence under filtered ultra-violet light. During heating on a hot-stage microscope, a phase change occurs between 270 and 275° and the material melts sharply at 282° (rate of heating, 4° a minute). Estriol is practically insoluble in water but is soluble in alcohol, dioxane and oils.

**Actions and Uses.**—Estriol is much less actively estrogenic than estrone when injected. See general statement on estrogen.

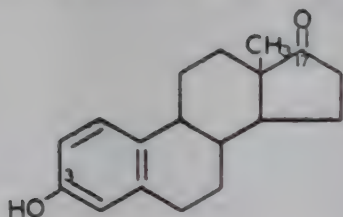
**Dosage.**—Orally, 0.06 to 0.12 mg. one to four times a day, alone or as supplement to parenteral therapy.

**PARKE, DAVIS & COMPANY**

**Kapseals Theelol:** 0.24 mg.

**ESTRONE-U.S.P.**—Estrugenone (KREMERS-URBAN).—Estrusol (CARROLL DUNHAM SMITH).—Thelestrin (CARRICK).—Theelin.—

The structural formula of estrone may be represented as follows:



**Physical Properties.**—Estrone occurs as a white to creamy white, crystalline powder or as small, white crystals. It is odorless and is stable in air. It is soluble in alcohol, acetone, dioxane, vegetable oils and in solutions of fixed alkali hydroxides but only slightly soluble in water.

**Actions and Uses.**—See the general statement on estrogen.

**Dosage.**—In disturbances of the menopause 0.2 mg. to 1 mg. injected intramuscularly one or more times weekly depending on the response of the patient. After relief is obtained dosage may be lowered to a maintenance level. As much as 5 mg. per week may be required in resistant cases of kraurosis vulvae. Estrone suppositories are valuable adjuncts in the treatment of senile vaginitis.

Occasionally, considerable uterine bleeding occurs in menopausal women following large doses of estrone. This may be quite alarming and it is advisable to reduce the dose of estrone as soon as feasible.

Estrone is effective by mouth if the dosage is adequate.

#### ABBOTT LABORATORIES

**Solution Estrone in Oil:** 1 cc. ampuls. A solution in peanut oil containing 0.2 mg., 0.5 mg. or 1 mg. of estrogenic activity in each cubic centimeter.

10 cc. vials. A solution in peanut oil containing 1 mg. of estrogenic activity in each cubic centimeter. The 10 cc. vial is preserved with 0.5 per cent chlorobutanol.

**Aqueous Suspension Estrone:** 1 cc. ampuls and 10 cc. vials. A suspension containing 2 mg. of estrogenic activity in each cubic centimeter.

5 cc. vials. A suspension containing 5 mg. of estrogenic activity in each cubic centimeter. Vial solutions are preserved with 0.9 per cent benzyl alcohol.

#### THE BIO-INTRASOL LABORATORIES, INC.

**Solution Estrone in Oil with Benzyl Alcohol 2%:** 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Aqueous Suspension Estrone:** 10 cc. vials. A suspension containing 2 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent phenol.



**BIORGANIC LABORATORIES, INC.**

**Powder Estrone:** Bulk; 1 Gm., 5 Gm. and 10 Gm. containers for compounding use.

**G. W. CARNRICK COMPANY**

**Solution Thelestrin in Oil:** 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter. The 10 cc. vial is preserved with 0.5 per cent benzyl alcohol.

**Aqueous Suspension Thelestrin:** 10 cc. vials. A suspension containing 1 mg. of estrone in each cubic centimeter.

1 cc. ampuls and 10 cc. vials. A suspension containing 2 mg. of estrone in each cubic centimeter.

10 cc. vials. A suspension containing 5 mg. of estrone in each cubic centimeter. The 10 cc. vials are preserved with thimerosal 1:10,000.

**KREMERS-URBAN COMPANY**

**Solution Estrugenone in Oil:** 1 cc. ampuls and 10 cc. and 30 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

10 cc. vials. A solution in sesame oil containing 2 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Suspension Estrugenone with Procaine Hydrochloride 1%:** 1 cc. ampuls and 10 cc. vials. A suspension in 15 per cent propylene glycol containing 2 mg. of estrone in each cubic centimeter. Preserved with thimerosal 1:10,000.

1 cc. ampuls and 5 cc. and 10 cc. vials. A suspension in 30 per cent propylene glycol containing 5 mg. of estrone in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite and thimerosal 1:10,000.

U. S. trademark 377,549.

**ELI LILLY & COMPANY**

**Aqueous Suspension Estrone:** 1 cc. ampuls. A suspension containing 1 mg., 2 mg. or 5 mg. of estrogenic activity in each cubic centimeter.

10 cc. ampuls. A suspension containing 2 mg. of estrone in each cubic centimeter.

5 cc. ampuls. A suspension containing 5 mg. of estrone in each cubic centimeter. Preserved with thimerosal 1:10,000.

**Solution Estrone in Oil:** 1 cc. ampuls. A solution in sesame oil containing 0.2 mg., 0.5 mg. or 1 mg. of estrogenic activity in each cubic centimeter.

10 cc. vials. A solution in sesame oil containing 1 mg. of estrogenic activity in each cubic centimeter.

**Vaginal Suppositories Estrone:** 0.2 mg. of estrogenic activity in a glycerin base.

**MEYER CHEMICAL COMPANY, INC.**

**Solution Estrone in Oil:** 10 cc. vials. A solution in sesame oil containing 1 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**E. S. MILLER LABORATORIES, INC.**

**Aqueous Suspension Estrone:** 10 cc. vials. A suspension containing 2 mg. or 5 mg. of estrone in each cubic centimeter.

**PARKE, DAVIS & COMPANY**

**Solution Theelin in Oil:** 1 cc. ampuls. A solution in peanut oil containing 0.2 mg., 0.5 mg. or 1 mg. of estrogenic activity in each cubic centimeter.

10 cc. vials. A solution in peanut oil containing 1 mg. of estrogenic activity in each cubic centimeter.

**Aqueous Suspension Theelin:** 1 cc. ampuls. A suspension containing 1 mg., 2 mg. or 5 mg. of estrogenic activity in each cubic centimeter.

5 cc. vials. A suspension containing 5 mg. of estrogenic activity in each cubic centimeter.

10 cc. vials. A suspension containing 2 mg. of estrogenic activity in each cubic centimeter. The 5 cc. and 10 cc. vials are preserved with benzethonium chloride 1:10,000.

**Vaginal Suppositories Theelin:** 0.2 mg. in glycerogelatin base.

**CARROLL DUNHAM SMITH PHARMACAL COMPANY**

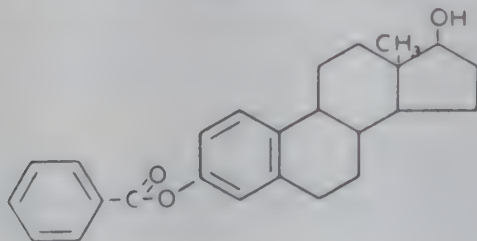
**Solution Estrusol in Oil:** 1 cc. ampuls and 30 cc. vials. A solution in peanut oil containing 1 mg. of estrone in each cubic centimeter. The 30 cc. vial is preserved with 0.5 per cent chlorobutanol.

**Aqueous Suspension Estrusol:** 1 cc. ampuls, 5 cc. and 15 cc. vials. A suspension in isotonic sodium chloride solution containing 2 mg. of estrone in each cubic centimeter.

5 cc. and 15 cc. vials. A suspension in isotonic sodium chloride solution containing 5 mg. of estrone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

***Esterified Parent Estrogens***

**ESTRADIOL BENZOATE-U.S.P.**—Dimenformon Benzoate (ORGANON).—Ovocycin Benzoate (CIBA).—Alpha-estradiol benzoate.— $\Delta$ -1,3,5-Estratriene-17-ol-3-benzoate.—The structural formula of estradiol benzoate may be represented as follows:



**Physical Properties.**—Estradiol benzoate is a white or slightly yellow-to-brownish, crystalline powder. It is odorless and stable in air. It is almost insoluble in water, soluble in alcohol, slightly soluble in ether and sparingly soluble in sesame and other vegetable oils.

**Actions and Uses.**—Estradiol benzoate, one of the esters of estradiol, is less subject to destruction in the tissues than its parent compound, and it is thus suitable for parenteral injection, producing the same effects as estradiol. (See the monograph on estradiol, the general statement on ovaries and the subsection on estrogen.) Esterification of estradiol slows its rate of absorption and elimination, so that the relative efficiency of the injectable estradiol benzoate is greater than that of orally administered estradiol. Estradiol benzoate is subject to the same contraindications as other estrogens.

**Dosage.**—Estradiol benzoate is administered by intramuscular injection as a solution in oil. Doses are expressed in terms of the weight of the esters.

For treatment of the menopausal syndrome, the initial dosage, depending on severity of symptoms, ranges from 1 to 1.66 mg. twice weekly for two or three injections; for maintenance, from 0.33 to 1 mg. twice weekly. In hypogenitalism and sexual infantilism, substitution therapy with doses of 1.66 mg. two or three times weekly is recommended. In functional uterine bleeding, 1.66 mg. three times weekly is recommended, followed by sequential progesterone therapy. In breast engorgement, 1.66 mg. daily is administered until the engorgement subsides. In kraurosis vulvae and senile vaginitis or pruritus vulvae, the dosage is the same as that indicated for the menopausal syndrome, except that this is sometimes supplemented by local therapy with vaginal suppositories of other estrogenic compounds. For palliation of prostatic carcinoma, 1.66 mg. is injected three times weekly.

#### CIBA PHARMACEUTICAL PRODUCTS, INC.

**Solution Ovocylin Benzoate in Oil:** 10 cc. vials. A solution in sesame oil containing 0.33 mg. or 1.66 mg. of estradiol benzoate in each cubic centimeter.

U. S. patent 2,033,487.

#### ORGANON, INC.

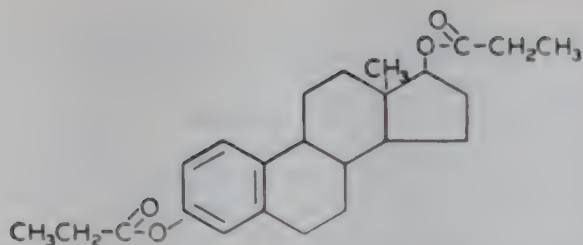
**Solution Dimenformon Benzoate in Oil:** 1 cc. ampuls. A solution in sesame oil containing 0.166, 0.33, 1 or 1.66 mg. of estradiol benzoate in each cubic centimeter. Preserved with 0.8 per cent methylparaben and 0.1 per cent propylparaben.

10 cc. vials. A solution in sesame oil containing 0.33 or 2 mg. of estradiol benzoate in each cubic centimeter. Preserved with 0.8 per cent methylparaben and 0.1 per cent propylparaben.

U. S. trademark 365,455.

**ESTRADIOL DIPROPIONATE.**—Ovocylin Dipropionate (CIBA).— $\Delta$ -1,3,5-Estratriene-3,17-dipropionate.—The structural formula of estradiol dipropionate may be represented as follows:





**Physical Properties.**—Estradiol dipropionate forms small, white to off white crystals. It is almost insoluble in water, soluble in acetone, alcohol and dioxane and sparingly soluble in vegetable oils. Estradiol dipropionate melts between 103 and 106°.

**Actions and Uses.**—Estradiol dipropionate, an ester of estradiol less subject to destruction in the tissues than the parent compound, is suitable for parenteral injection to produce the effects of that estrogen and shares the actions and uses of estrogens in general. Its contraindications are also the same as for other estrogens. See the monograph for estradiol, the general statement on the ovaries and the subsection on estrogen.

Estradiol dipropionate, like estradiol benzoate, is absorbed more slowly and eliminated less rapidly than estradiol, but its effects are qualitatively the same as those of other estradiol compounds. Also see the monograph on estradiol benzoate.

**Dosage.**—Estradiol dipropionate is injected intramuscularly as a solution in oil and is given in doses expressed in terms of the weight of the ester. A single dose is approximately half as potent by weight as estradiol benzoate, but, owing to its more sustained action, estradiol dipropionate is more potent than the benzoate when the two are compared on the basis of maintenance dosage required to provide equivalent therapeutic effects.

For the menopausal syndrome, the initial dosage ranges from 1 to 5 mg. injected weekly for two or three injections; maintenance usually requires from 1 to 2.5 mg. every 10 to 14 days. For substitution therapy in hypogenitalism and sexual infantilism, 2.5 to 5 mg. weekly is recommended. For functional uterine bleeding, 5 mg. weekly is recommended followed by sequential progesterone therapy. In breast engorgement, 2.5 mg. daily is given until the condition subsides. The same doses as for the menopausal syndrome are applicable to kraurosis vulvae and senile vaginitis or pruritus vulvae. Systemic therapy may be supplemented by the local use of vaginal suppositories of estradiol. As a palliative in prostatic carcinoma, 5 mg. weekly is recommended; in mammary cancer, 5 mg. twice weekly by intramuscular injection.

#### CIBA PHARMACEUTICAL PRODUCTS, INC.

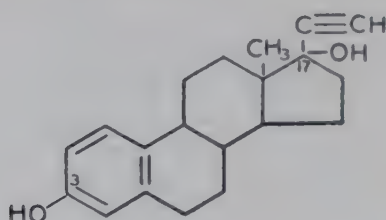
**Solution Ovocycin Dipropionate in Oil:** 1 cc. ampuls. A solution in sesame oil containing 0.2 mg., 0.5 mg., 1 mg., 2.5 mg. or 5 mg. of estradiol dipropionate in each cubic centimeter.

10 cc. vials. A solution in peanut oil containing 0.2 mg., 1 mg. or 5 mg. of estradiol dipropionate in each cubic centimeter.

U. S. patent 2,205,627.

### Derivatives of Parent Estrogens

**ETHINYL ESTRADIOL.**—Estinyl (SCHERING).—Eticylol (CIBA).—Lynoral (ORGANON).—Oradiol (VANPELT & BROWN).—Orestralyne (MCNEIL). — 17-Ethinyl-3,17-estradiol. — 17-Ethinyl-3,17-dihydroxy- $\Delta$ -1,3,5-estratriene.—The structural formula of ethinyl estradiol may be represented as follows:



Ethinyl estradiol may be prepared by the action of potassium acetylide upon estrone in liquid ammonia, followed by evaporation of the ammonia, solution in water and precipitation with mineral acid. The product is purified by recrystallization from methanol. When assayed biologically in rats by the Allen-Doisy method, ethinyl estradiol exhibits a potency of approximately 100,000 I. U. per milligram.

**Physical Properties.**—Ethinyl estradiol is a fine, white, odorless, crystalline powder, which melts between 141 and 146°. On prolonged heating at 150° the melt sometimes solidifies. The polymorph thus obtained melts between 180 and 186°. It is soluble in acetone, alcohol, chloroform, dioxane, ether and vegetable oils, but practically insoluble in water. It is soluble in solutions of sodium or potassium hydroxide.

**Actions and Uses.**—The ethinyl radical delays the decomposition of the estradiol molecule in the stomach, intestine and liver, so that the drug can be given orally; it is one of the most potent estrogens known. In the female it compensates for deficiencies in estrogen production; in the male it opposes some of the actions of the androgens, as in prostatic carcinoma. The incidence of side reactions, such as headache, nausea and vomiting, is found in the same proportion of patients as occurs with other orally active estrogens. When the total daily dose is taken at bedtime the incidence of side reactions is reduced.

**Dosage.**—In hypo-ovarianism: 0.05 mg. one to three times daily during the first half of a cyclic estrogen-progesterone regime. In menopause: 0.02 to 0.05 mg. one to three times daily.

For functional uterine bleeding (menometrorrhagia), 0.5 mg. once or twice daily. After hemostasis, 0.05 mg. one to three times daily as part of cyclic estrogen-progesterone therapy. The suggested course of therapy consists of three 30-day cycles exactly alike. The first cycle begins as soon as diagnosis is made. From the first to the fifteenth day ethinyl estradiol is used alone. From the sixteenth to the twentieth day the patient receives in addition a daily intra-

muscular injection of 5 mg. of progesterone. The treatment is then suspended, and after a latent period of about 5 days the patient generally begins to bleed again. Five additional days are allowed for this bleeding episode, and then the second cycle of treatment is begun.

In prostatic carcinoma, 0.15 to 3 mg. daily. For control of breast engorgement: 0.2 to 1 mg. daily for 3 days, gradually decreasing to 0.1 mg. daily at the end of an additional 7 days when the treatment should be discontinued to avoid reinitiation of lactation or increase in lochia. Exact dosage for this form of treatment has not been established. For palliation of mammary cancer, 3 mg. daily by mouth.

#### BIORGANIC LABORATORIES, INC.

Crystalline Ethinyl Estradiol: Bulk; for manufacturing use only.

#### CHEMO PURO MANUFACTURING CORPORATION

Powder Ethinyl Estradiol: Bulk; for manufacturing use.

#### CIBA PHARMACEUTICAL PRODUCTS

Tablets Eticylol: 0.02 mg. and 0.05 mg.

#### MCNEIL LABORATORIES, INC.

Elixir Orestralyn: 118.3 cc., 473 cc. and 3.78 liter bottles. A flavored alcoholic elixir containing 0.004 mg. of ethinyl estradiol in each cubic centimeter.

Tablets Orestralyn: 0.02 mg., 0.05 mg. and 0.5 mg.

U. S. trademark 560,766.

#### ORGANON, INC.

Elixir Lynoral: 118 cc., 473 cc. and 3.78 liter bottles. A solution containing 0.0075 mg. of ethinyl estradiol in each cubic centimeter. Preserved with 0.037 per cent methylparaben and 0.025 per cent propylparaben.

Tablets Lynoral: 0.01 mg. and 0.05 mg.

#### SCHERING CORPORATION

Tablets Estinyl: 0.02 mg., 0.05 mg. and 0.5 mg.

U. S. patents 2,251,939 and 2,265,976. U. S. trademark 398,209.

#### VANPELT & BROWN, INC.

Tablets Oradiol: 0.02 mg. and 0.05 mg.

U. S. trademark 568,045.

### *Conjugated Estrogens*

ESTROGENIC SUBSTANCES, CONJUGATED. — Amnestrogen (SQUIBB). — Conestron (WYETH). — Estrifol (PREMO). — Hormesteral (MILLER). — Konogen (LILLY). — Premarin (AYERST). — An amor-



phous preparation containing the naturally occurring, water-soluble, conjugated forms of the mixed estrogens obtained from the urine of pregnant mares. Conjugated estrogenic substances may be prepared by either selective extraction or selective adsorption of concentrated urine from mares pregnant five months or longer.

The principal estrogen present in conjugated estrogenic substances is sodium estrone sulfate. Varying small amounts of other equine estrogens and relatively large quantities of nonestrogenic material are also present in the mixture. The total estrogenic potency of the preparation is expressed in terms of an equivalent quantity of sodium estrone sulfate.

**Actions and Uses.**—See the general statement on estrogen.

**Dosage.**—For the control of menopausal symptoms, 1.25 mg. daily is usually sufficient. If the response is not satisfactory after a few days of treatment, the dose may be increased. After symptoms have been brought under control the dosage may usually be reduced. For the treatment of senile vaginitis, kraurosis vulvae and pruritus vulvae, 1.25 to 3.75 mg. daily should be sufficient. For palliation of mammary cancer, a daily oral dose of 30 mg. is recommended.

#### AYERST LABORATORIES, INC.

**Liquid Premarin:** 120 cc. bottles. A 12.5 alcohol solution containing 0.16 mg. of conjugated estrogenic substances in each cubic centimeter.

**Tablets Premarin:** 0.63 mg., 0.3 mg., 1.25 mg. and 2.5 mg.  
U. S. trademark 397,925.

#### ELI LILLY & COMPANY

**Tablets Konogen:** 0.625 mg., 1.25 mg. and 2.5 mg.

#### E. S. MILLER LABORATORIES, INC.

**Tablets Hormesteral:** 1.25 mg.

#### PREMO PHARMACEUTICAL LABORATORIES, INC.

**Tablets Estrifol:** 1.25 mg.

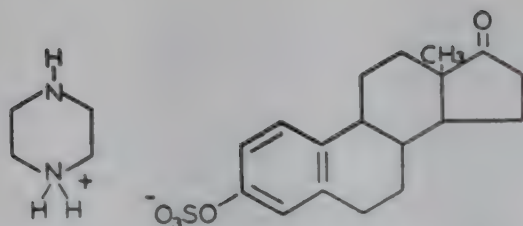
#### E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Tablets Amnestrogen:** 0.3 mg., 0.62 mg., 1.25 mg. and 2.5 mg.  
U. S. trademark 529,515.

#### WYETH LABORATORIES, INC.

**Tablets Conestron:** 0.62 mg. and 1.25 mg.  
U. S. trademark 422,035.

**PIPERAZINE ESTRONE SULFATE.**—Sulestrex Piperazine (ABBOTT).—Piperazine estrone sulfate marketed for use as a drug is stabilized with a small amount of free piperazine.—The structural formula of piperazine estrone sulfate may be represented as follows:



**Physical Properties.**—Piperazine estrone sulfate is a fine, white to creamy white, odorless, crystalline powder. It melts between 185 and 195° to a light brown syrup, which solidifies on further heating, and finally melts with decomposition between about 240 and 250°. It is slightly soluble in water and alcohol.

**Actions and Uses.**—Piperazine estrone sulfate has the same actions and uses as the naturally occurring conjugated estrogens. See the general statement on estrogens.

**Dosage.**—Piperazine estrone sulfate is administered orally. For the control of menopausal symptoms, 1.5 mg. daily is usually sufficient. The dosage may be increased if the response is not satisfactory; it may be gradually reduced when the symptoms have been controlled. For the treatment of senile vaginitis, kraurosis vulvae and pruritus vulvae, 1.5 to 4.5 mg. should be adequate. For post-partum breast engorgement, 4.5 mg. is administered at 4-hour intervals for five doses.

#### ABBOTT LABORATORIES

**Elixir Sulestrex Piperazine:** 118 cc. bottles. A flavored elixir containing 0.3 mg. of piperazine estrone sulfate in each cubic centimeter.

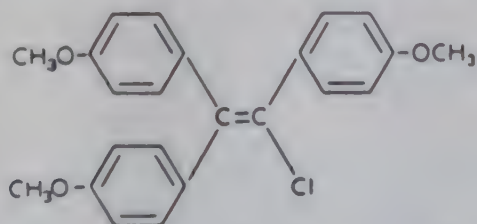
**Tablets Sulestrex Piperazine:** 0.75 mg., 1.5 mg. and 3 mg.

U. S. patent 2,642,427. U. S. trademark 560,753.

## Non-Steroid Estrogens

### Stilbene Derivatives

**CHLOROTRIANISENE.**—TACE (MERRELL).—Chlorotris (*p*-methoxyphenyl)ethylene.—Tri-*p*-anisylchloroethylene.—The structural formula of chlorotrianisene may be represented as follows:



**Physical Properties.**—Chlorotrianisene is a white, odorless, crystalline powder with a melting point between 114 and 117° (becomes syrupy at about 108°). It is freely soluble in acetone,

benzene and chloroform and very slightly soluble in water. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 0.28 Gm. in alcohol and 3.6 Gm. in ether.

**Actions and Uses.**—Chlorotrianisene in general shares the actions and uses of the estrogens (see the general statement on estrogens). However, it possesses certain peculiar attributes not common to other estrogens. When administered orally, the amount of estrogenic activity recovered in the stool exceeds the amount originally administered in the form of chlorotrianisene. This indicates that by some metabolic process the potency of the drug is enhanced. A hint at the probable locale of this enhancement is furnished by experiments in which the activity of chlorotrianisene is increased by incubation with liver homogenates. Chlorotrianisene, in the dosages used in experimental studies on laboratory animals, apparently induced less pituitary or adrenal hyperplasia than other estrogens. The compound is stored in the body fat, from which it is slowly released over a period of time, varying with the amount administered. Therefore, its action will persist for varying periods following discontinuance of the drug. Its use in high dosages in mammary cancer occurring 5 years or more past the menopause is not recommended because of the occurrence of uterine bleeding, although there is less tendency toward withdrawal bleeding in the lower dosage recommended for the menopause. Chlorotrianisene is effective in the relief of breast engorgement. It apparently causes a minimal incidence of withdrawal bleeding.

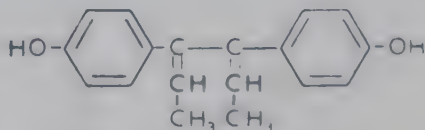
**Dosage.**—Chlorotrianisene has a lower milligram equivalent than other synthetic estrogens and doses are higher for comparable effects. The average dose for relief of menopausal symptoms varies between 12 and 24 mg. daily by mouth. In prostatic cancer, 24 mg. daily has proved effective in relieving symptoms. The average recommended dose for the relief of breast engorgement is 48 mg. of chlorotrianisene daily for 7 days.

THE WM. S. MERRELL COMPANY

Capsules TACE: 12 mg. in corn oil.

U. S. patent 2,430,891.

**DIENESTROL.**—Restrol (CENTRAL).—*p,p'*-(Diethylideneethylene)-diphenol.—The structural formula of dienestrol may be represented as follows:



**Physical Properties.**—Dienestrol forms colorless or white needle-like crystals or a white crystalline powder. It melts between 231 and 234°. It is readily soluble in acetone, alcohol, ether, methanol and propylene glycol and in dilute aqueous sodium hydroxide; it is soluble in chloroform and practically insoluble in water and dilute mineral acids.



**Actions and Uses.**—Dienestrol is used orally. Investigation indicates that this compound gives rise to fewer side reactions than diethylstilbestrol and related synthetic estrogens. See general statement on estrogen.

**Dosage.**—In the treatment of menopausal symptoms, orally in daily doses of 0.1 to 0.5 mg. for mild to moderately severe symptoms; or 2.5 to 5 mg. injected subcutaneously or intramuscularly, once or twice weekly. In artificially induced climacteric a daily oral dosage of 0.5 to 1.5 mg. may be necessary. For palliation of mammary cancer, 15 mg. is the daily oral dosage.

#### THE BIO-RAMO DRUG COMPANY

Tablets Dienestrol: 0.1 mg., 0.5 mg. and 1.5 mg.

#### THE CENTRAL PHARMACAL COMPANY

**Suspension Restrol:** 10 cc. vials. A suspension containing 5 mg. of dienestrol in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Restrol: 0.1 and 0.5 mg.

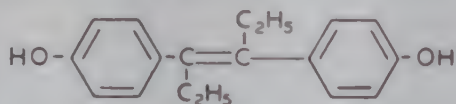
#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Dienestrol:** Bulk; for manufacturing use.

#### WHITE LABORATORIES, INC.

Tablets Dienestrol: 0.1 mg., 0.5 mg. and 10 mg.

**DIETHYLSTILBESTROL-U.S.P.**—Stilbestrol.— $\alpha, \alpha'$ -Diethyl-4,4'-stilbenediol.—“Diethylstilbestrol, dried at 105° for 4 hours, contains not less than 98.5 per cent of  $C_{18}H_{20}O_2$ .” *U. S. P.* The structural formula of diethylstilbestrol may be represented as follows:



**Physical Properties.**—Diethylstilbestrol is a white, odorless, crystalline powder, melting between 169 and 172°. It is almost insoluble in water but is soluble in alcohol, fat solvents and fatty oils and in dilute alkali hydroxides. It should be stored in tight, light-resistant containers.

**Actions and Uses.**—Dodds and his co-workers, after extensive experimentation with synthetic substances, recognized the estrogenic activity of the stilbene compounds. Diethylstilbestrol is the most potent of these products described up to the present time. It may be prepared in a variety of ways from nonbiologic, organic chemicals. Its physiologic activity duplicates practically all the known actions of natural estrogens. Thus it induces estrus in rodents, stimulates the growth of the endometrium and myometrium, primes the endometrium for progestational changes, causes reddening of the “sex skin” of monkeys and feminization of the plumage of birds, induces growth of mammary ducts in female and male animals as well as in human beings, raises the blood fat and

calcium in fowl, induces withdrawal uterine bleeding in castrate animals and human beings and suppresses ovulation. It also inhibits the secretion of various factors of the anterior pituitary gland in experimental animals. It differs in its action from natural estrogens in its inability to cause the ovipositor reaction of the female bitterling and to antagonize the action of androgens on comb growth of capons. Various modifications of diethylstilbestrol have been devised, such as fatty acid esters and a number of ethers, for increasing the estrogenic efficiency of this substance.

Diethylstilbestrol possesses the advantage of being highly active by mouth as well as percutaneously. The ratio of potency between oral and parenteral administration varies in the hands of different investigators from 1:2 to 1:5 in the human being as well as in rodents. In the therapeutic use of diethylstilbestrol there may be a significant incidence of side reactions, the most common of these being nausea, vomiting and headache. There is, however, conclusive evidence that experimentally diethylstilbestrol is not significantly more toxic than the natural estrogens. It is now believed that the unpleasant symptoms arising from diethylstilbestrol administration are systemic rather than local in origin, and probably due to its rapid absorption into the blood stream, since few untoward symptoms are observed with the use of diethylstilbestrol compounds, which are slowly absorbed from the site of administration.

For uses and contraindications see the general statement on estrogen.

**Dosage.**—The average therapeutic dose for the treatment of menopausal symptoms is 0.5 to 1 mg. daily by mouth, although it is advisable to start with smaller doses for patients who tend to develop disagreeable symptoms. In other conditions, courses of therapy a few weeks apart are recommended by some authorities. Injection of similar quantities of diethylstilbestrol in oil solution are administered one or more times weekly. Ointment or suppositories containing this material may be used for topical applications in the treatment of vulvar and vaginal conditions. In prostatic carcinoma, the recommended dosage is 3 mg. daily intramuscularly for several weeks if oral administration is not feasible, after which the dosage is gradually reduced to 1 mg. daily, or 0.5 mg. three times daily by mouth. For palliation of mammary cancer, 15 mg. is the daily oral dose recommended.

#### ABBOTT LABORATORIES

**Solution Diethylstilbestrol in Oil:** 1 cc. ampuls. A solution in peanut oil containing 5 mg. of diethylstilbestrol in each cubic centimeter.

**Tablets Diethylstilbestrol:** 0.5 mg., 1 mg. and 5 mg.

**Vaginal Suppositories Diethylstilbestrol:** 0.5 mg.

#### AMERICAN PHARMACEUTICAL COMPANY, INC.

**Tablets Diethylstilbestrol:** 0.5 mg., 1 mg. and 5 mg.

**BIO-INTRASOL LABORATORIES, INC.**

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in sesame oil containing 1 mg. of diethylstilbestrol in each cubic centimeter.

**THE BOWMAN BROS. DRUG COMPANY**

Tablets Diethylstilbestrol: 5 mg.

**BOYLE & COMPANY**

Tablets Diethylstilbestrol: 5 mg.

**CHICAGO PHARMACAL COMPANY**

Tablets Diethylstilbestrol: 1 mg. and 5 mg., uncoated; 0.25 mg., 0.5 mg., 1 mg. and 5 mg., sugar coated.

**COLE CHEMICAL COMPANY**

Tablets Diethylstilbestrol: 1 mg.

**THE DRUG PRODUCTS COMPANY, INC.**

Pulvoids Diethylstilbestrol: 0.1 mg. and 1 mg.

**ENDO PRODUCTS, INC.**

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in sesame oil containing 0.5 mg., 1 mg., 2 mg. and 5 mg. of diethylstilbestrol in each cubic centimeter.

**ESTRO CHEMICAL COMPANY, INC.**

Solution Diethylstilbestrol in Oil: 1 cc. ampuls and 30 cc. vials. A solution in corn oil containing 1 mg., 2 mg. and 5 mg. of diethylstilbestrol in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**GOLD LEAF PHARMACAL COMPANY, INC.**

Solution Diethylstilbestrol in Oil: 1 cc. ampuls and 30 cc. vials. A solution in sesame oil containing 1 mg. and 5 mg. of diethylstilbestrol in each cubic centimeter. The vials are preserved with 0.5 per cent chlorobutanol.

**KEITH-VICTOR PHARMACAL COMPANY**

Tablets Diethylstilbestrol: 5 mg.

**ELI LILLY & COMPANY**

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in cottonseed oil containing 1 mg. or 5 mg. of diethylstilbestrol in each cubic centimeter.

Suppositories Diethylstilbestrol: 0.1 and 0.5 mg.

Tablets Diethylstilbestrol: 0.1 mg., 0.25 mg., 0.5 mg., 1 mg. and 5 mg.



## PAUL MANEY LABORATORIES, INC.

Tablets Diethylstilbestrol: 0.1 mg., 0.25 mg., 0.5 mg., 1 mg. and 5 mg.

## E. S. MILLER LABORATORIES, INC.

Solution Diethylstilbestrol in Oil with Benzocaine 2%: 1 cc. ampuls. A solution in sesame oil containing 0.5 mg. of diethylstilbestrol in each cubic centimeter with 2 per cent benzocaine. Preserved with 0.5 per cent cresol.

Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg. and 1 mg.

## PHYSICIANS' DRUG AND SUPPLY COMPANY

Tablets Diethylstilbestrol: 0.2 mg., 0.5 mg., 1 mg. and 5 mg.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in peanut oil containing 5 mg. of diethylstilbestrol in each cubic centimeter.

Tablets Diethylstilbestrol: 1 mg. and 5 mg.

Vaginal Suppositories Diethylstilbestrol: 0.1 mg. and 0.5 mg.

## WILLIAM H. RORER, INC.

Tablets Diethylstilbestrol: 1 mg. and 5 mg.

## CARROLL DUNHAM SMITH PHARMACAL COMPANY

Tablets Diethylstilbestrol: 5 mg.

## THE UPJOHN COMPANY

Perles Diethylstilbestrol: 0.1 mg., 0.25 mg., 0.5 mg., 1 mg. and 5 mg.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in cottonseed oil containing 1 mg. of diethylstilbestrol in each cubic centimeter.

## THE VALE CHEMICAL COMPANY, INC.

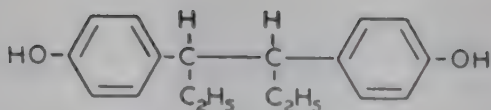
Tablets Diethylstilbestrol: 0.1 mg., 0.5 mg. and 1 mg.

## WINTHROP-STEARNES, INC.

Solution Diethylstilbestrol in Oil: 1 cc. ampuls. A solution in sesame oil containing 0.5 mg. or 1 mg. of diethylstilbestrol in each cubic centimeter.

Tablets Diethylstilbestrol: 5 mg.

HEXESTROL.—*p,p'*-(1,2-Diethylethylene)diphenol.—*meso*-3,4-Di-*p*-hydroxyphenyl-*n*-hexane.—The structural formula of hexestrol may be represented as follows:



It may be prepared from anethole in ether solution by (a) treating with anhydrous hydrogen bromide to form anethole hydrobromide, (b) conversion of the anethole hydrobromide to 3,4-dianisylhexane by means of metallic magnesium, aluminum, copper or zinc turnings and (c) hydrolysis of the 3,4-dianisylhexane to form hexestrol. The product thus obtained may be purified by recrystallization from dilute alcohol.

**Physical Properties.**—Hexestrol is an odorless, white, crystalline powder which melts between 185 and 188°. It is freely soluble in ether; soluble in acetone, alcohol and methanol; slightly soluble in benzine and chloroform; and practically insoluble in water and dilute mineral acids. It dissolves in vegetable oils and in dilute sodium or potassium hydroxide. When recrystallized from diluted alcohol, hexestrol forms thin, platelike crystals of irregular, serrated outline.

**Actions and Uses.**—Hexestrol is used for the same conditions for which estrogenic substances are employed and the contraindications are those for natural estrogens. See the general statement on estrogen. Incidence of toxic symptoms is lower than that following administration of diethylstilbestrol.

**Dosage.**—As is the case with all estrogenic substances, the dosage of hexestrol must be adjusted to the individual case. As a guide the following dosages are suggested: For menopausal symptoms, 2 to 3 mg. daily by mouth until symptoms are under control, and then 0.2 to 1 mg. daily as a maintenance dose; or by injection, 1 mg. in oil three times weekly with similar lowering for maintenance of control. For senile vaginitis and kraurosis vulvae, 2 to 3 mg. daily by mouth, or 1 mg. in oil three times weekly by injection.

CHEMO PURO MANUFACTURING CORPORATION

Powder Hexestrol: Bulk; for manufacturing use.

S. E. MASSENGILL COMPANY

Tablets Hexestrol: 3 mg.

THE WM. S. MERRELL COMPANY

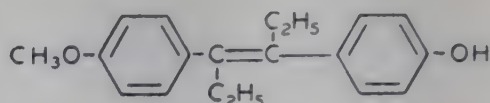
Solution Hexestrol in Oil: 20 cc. vials. A solution in vegetable oil containing 1 mg. or 5 mg. of hexestrol in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Hexestrol: 1 mg. and 3 mg.

PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Hexestrol: 1 mg. and 3 mg.

**MESTILBOL.**—Monomestrol (WALLACE & TIERNAN).— $\alpha, \alpha'$ -Diethyl-4'-methoxy-4-stilbenol.—Diethylstilbestrol monomethyl ether.—The structural formula of mestilbol may be represented as follows:



It may be prepared by methylation of diethylstilbestrol or by partial demethylation of the dimethyl ether of diethylstilbestrol. The crude product may be purified by distillation in vacuum and by recrystallization from water-alcohol or benzene-petroleum ether mixtures.

**Physical Properties.**—Mestilbol is an odorless, white, crystalline powder, which melts between 116 and 117° after recrystallization from benzene-petroleum ether, and between 112 and 114° after recrystallization from alcohol. It is soluble in alcohol; freely soluble in acetone and ether; and practically insoluble in water, dilute mineral acids and dilute aqueous solutions of sodium and potassium hydroxide. It dissolves in vegetable oils and in dilute solutions of sodium or potassium hydroxide in diluted alcohol.

**Actions and Uses.**—See the general statement on estrogen. Patients undergoing treatment should remain under constant medical supervision. Side effects are rare, and when they do occur they are usually mild, although in a few instances it may be necessary to reduce the dosage temporarily.

**Dosage.**—The average oral dose for the treatment of menopausal symptoms is 0.5 to 1 mg. daily although if necessary 10 to 25 mg. may be given parenterally biweekly. Dosage for atrophic genital disorders such as kraurosis vulvae is 1 to 5 mg. daily by mouth or 25 mg. weekly by parenteral injection; for the prevention of breast engorgement 5 to 10 mg. daily or 25 mg. the first and third days by injection; for prostatic cancer 2.5 mg. three times daily by mouth. The duration of treatment varies in the menopause; it is a few months for atrophic genital disorders, 3 to 5 days for prevention of breast engorgement and continuous for prostatic cancer.

WALLACE & TIERNAN, INC.

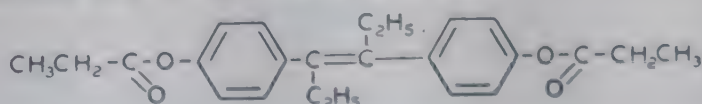
**Solution Monomestrol in Oil:** 1 cc. ampuls. A solution in sesame oil containing 10 mg. or 25 mg. of mestilbol in each cubic centimeter.

**Tablets Monomestrol:** 0.25, 0.5, 1 and 2.5 mg.

U. S. patent 2,385,468. U. S. trademark 397,572.

### Esterified Stilbene Derivatives

**DIETHYLSTILBESTROL DIPROPIONATE.**— $\alpha,\alpha'$ -Diethyl-4,4'-stilbenediol dipropionate.—The structural formula of diethylstilbestrol dipropionate may be represented as follows:



**Physical Properties.**—Diethylstilbestrol dipropionate is an odorless, tasteless, white, crystalline powder which melts between 105



and 107°. It is readily soluble in acetone, hot alcohol, benzene, chloroform, ether and hot methanol, soluble in vegetable oils, very slightly soluble in water and dilute mineral acids and insoluble in aqueous alkalis. A suspension of 0.1 Gm. of diethylstilbestrol dipropionate in 10 ml. of diluted alcohol is neutral to litmus paper.

**Actions and Uses.**—Diethylstilbestrol dipropionate is used for the same conditions for which estrogenic substances are employed, although when the drugs are administered intramuscularly in oil, reactions such as nausea and vomiting are less frequent with a dipropionate salt than with free diethylstilbestrol. Diethylstilbestrol dipropionate is relatively slowly absorbed from the oil depot and causes a lower blood stream concentration, although one of longer duration.

**Dosage.**—Diethylstilbestrol dipropionate in oil is administered intramuscularly, with the ratio of potency between oral and parenteral administration varying from 1:2 to 1:5. The following average dosages should be modified to meet individual requirements:

Menopause } from 0.5 to 2 mg. intramuscularly two or three  
Senile vaginitis } times a week.

Relief of breast engorgement—5 mg. intramuscularly once or twice daily for 2 to 4 days.

Carcinoma of the prostate—3 mg. intramuscularly each day for about 10 days.

After relief of symptoms the dosage should be reduced until the minimum effective dose for maintenance has been established.

#### THE BLUE LINE CHEMICAL COMPANY

**Solution Diethylstilbestrol Dipropionate in Oil:** 10 cc. vials. A solution in peanut oil containing 1 or 5 mg. of diethylstilbestrol dipropionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Tablets Diethylstilbestrol Dipropionate:** 1 and 5 mg.

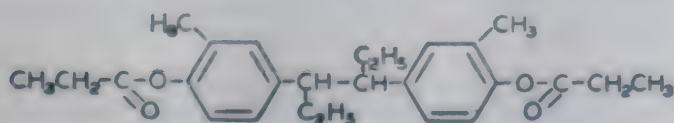
#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Diethylstilbestrol Dipropionate:** Bulk; for manufacturing use.

#### WINTHROP-STEARNES, INC.

**Solution Diethylstilbestrol Dipropionate in Oil:** 1 cc. ampuls. A solution in olive oil containing 0.5 mg., 1 mg., or 5 mg. of diethylstilbestrol dipropionate in each cubic centimeter.

**PROMETHESTROL DIPROPIONATE.**—Meprane Dipropionate (REED & CARRICK).—Dimethylhexestrol dipropionate.—4,4'-(1,2-Diethylethylene)di-*o*-cresol dipropionate.—The structural formula of promethestrol dipropionate may be represented as follows:



**Physical Properties.**—Promethestrol dipropionate is a white, odorless, crystalline powder, which melts between 113 and 116°. It is freely soluble in benzene, ether and ethyl acetate, slightly soluble in alcohol and practically insoluble in dilute acids, dilute alkalis and water. A solution of promethestrol dipropionate in 90 per cent alcohol is neutral to litmus.

**Actions and Uses.**—Promethestrol dipropionate is similar in its actions to diethylstilbestrol and other synthetic estrogens. See the general statement on estrogen.

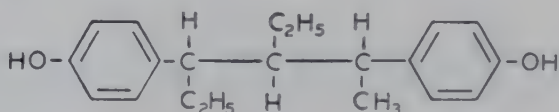
**Dosage.**—In the menopause, treatment may be started with 1 mg. given three times daily, gradually reducing the dosage to 1 mg. daily.

REED & CARNRICK

Tablets Meprane Dipropionate: 1 mg.

### Unclassified Derivatives of Non-Steroid Estrogens

**BENZESTROL.**—3-Ethyl-2,4-bis(*p*-hydroxyphenyl)hexane.—Benzestrol is one pair of racemates of the synthetic substance possessing the following structural formula:



**Physical Properties.**—Benzestrol is an odorless, white, crystalline powder which melts between 161 and 163°. It is readily soluble in acetone, alcohol, ether, methanol and sodium hydroxide T.S., soluble in vegetable oils, moderately soluble in glacial acetic acid, slightly soluble in dilute alcohol, benzene, chloroform and petroleum ether and practically insoluble in water and dilute mineral acids.

**Actions and Uses.**—See the general statement on estrogen. Incidence of toxicity is low with benzeestrol.

**Dosage.**—By biologic assay, 1 mg. of benzeestrol is equivalent to approximately 2.5 mg. of estrone. Average dosage for control of menopausal symptoms and senile vaginitis: orally, 2 to 3 mg.; by injection, 2 to 5 mg. This may be repeated daily for 4 to 7 days until the dosage requirement is determined by clinical observation. For relief of breast engorgement, 5 mg. orally, three or four times daily for 5 or 6 days may be given. For prostatic carcinoma, the recommended dosage is 5 to 15 mg. two or three times weekly by injection if oral administration is not feasible, after which the dosage is gradually reduced.

SCHIEFFELIN & COMPANY

**Elixir Benzestrol:** 473 cc. bottles. A flavored elixir containing 0.5 mg. of benzestrol in each cubic centimeter.

**Solution Benzestrol:** 10 cc. multiple dose vials. A solution containing 5 mg. of benzestrol in each cubic centimeter.

**Suspension Benzestrol with Benzyl Alcohol 2%:** 1 cc. ampuls and 10 cc. vials. An aqueous suspension containing 5 mg. of benzestrol in each cubic centimeter.

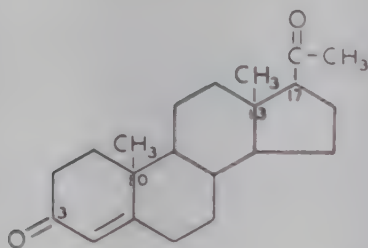
**Tablets Benzestrol:** 0.5 mg., 1 mg., 2 mg. and 5 mg.

**Vaginal Tablets Benzestrol:** 0.5 mg.

U. S. patents 2,400,033 and 2,400,034.

## Progesterone

**PROGESTERONE-U.S.P.—Corlutone (GOLD LEAF).—4-Pregnene-3,20-dione.**—The structural formula of progesterone may be represented as follows:



**Physical Properties.**—Progesterone occurs as a white, crystalline powder. It is colorless and is stable in air. Progesterone is practically insoluble in water; it is soluble in alcohol, in acetone and in dioxane. It is sparingly soluble in vegetable oils.

**Actions and Uses.**—Progesterone, originally obtained from the corpus luteum but now made synthetically, is of value in the treatment of functional uterine bleeding ("metropathia hemorrhagica"). Its use for the treatment of primary or secondary amenorrhea, with or without estrogen, is incompletely established. Although progesterone has long been employed in the treatment of threatened or habitual abortion, dysmenorrhea and menorrhagia, there is insufficient satisfactory evidence to establish its effectiveness for these conditions.

**Dosage.**—Progesterone is ineffective orally. It is administered either intramuscularly in oil solution or subcutaneously in aqueous suspension in doses up to 20 mg. daily.

### THE BIO-INTRASOL LABORATORIES, INC.

**Solution Progesterone in Oil with Benzyl Alcohol 2%:** 10 cc. vials. A solution containing 10 mg. or 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Aqueous Suspension Progesterone with Procaine Hydrochloride 1%:** 10 cc. vials. An aqueous suspension containing 10 mg. or 25 mg. of progesterone in each cubic centimeter. Preserved with thimerosal 1:10,000.

### BIOPHYSICS LABORATORIES, INC.

**Solution Progesterone in Oil with Benzyl Alcohol 2%:** 10 cc. vials.



A solution in sesame oil containing 25 mg. of progesterone in each cubic centimeter. Preserved with 0.004 per cent phenylmercuric benzoate.

**CARLO ERBA, INC.**

**Solution Progesterone in Oil:** 10 cc. vials. A solution in peanut oil containing 10 mg. or 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**GOLD LEAF PHARMACAL COMPANY, INC.**

**Solution Corlutone in Oil:** 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 10 and 25 mg. of progesterone in each cubic centimeter. The 10 cc. vials are preserved with 0.5 per cent chlorobutanol.

**KREMERS-URBAN COMPANY**

**Solution Progesterone in Oil:** 10 cc. vials. A solution in sesame oil containing 10 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Solution Progesterone in Oil with Benzyl Alcohol 5%:** 10 cc. vials. A solution in sesame oil containing 25 mg. of progesterone in each cubic centimeter.

**LINCOLN LABORATORIES, INC.**

**Aqueous Suspension Progesterone:** 10 cc. vials. A suspension containing 10 mg. of progesterone in each cubic centimeter of physiologic isotonic sodium chloride solution. Preserved with 1 per cent acacia and thimerosal 1:10,000.

**MEYER CHEMICAL COMPANY**

**Solution Progesterone:** 10 cc. vials. A solution in sesame oil containing 10 or 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**THE UPJOHN COMPANY**

**Solution Progesterone in Oil:** 1 cc. ampuls and 5 cc. vials. A solution in cottonseed oil containing 5 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

5 cc. vials. A solution in cottonseed oil containing 10 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Aqueous Suspension Progesterone:** 1 cc. and 10 cc. vials. A suspension in isotonic salt solution containing 25 mg. of progesterone in each cubic centimeter. Preserved with thimerosal 1:10,000.

**THE VITARINE COMPANY, INC.**

**Solution Progesterone in Oil:** 1 cc. ampuls. A solution in sesame oil containing 5 mg. or 10 mg. of progesterone in each cubic centimeter.

10 cc. vials. A solution in sesame oil containing 10 mg. of pro-

gesterone in each cubic centimeter. Both sizes preserved with 0.5 per cent chlorobutanol.

**Solution Progesterone in Oil with Benzyl Alcohol 3%:** 10 cc. vials. A solution in sesame oil containing 25 mg. of progesterone in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

## PANCREAS

The pancreas has two functions: (1) It secretes into the intestine a digestive juice containing the enzymes trypsin, lipase and amylase; (2) it secretes into the blood a hormone, insulin, which regulates carbohydrate metabolism.

Diabetes is a disease characterized by hyperglycemia due to insulin deficiency or possibly to other causes. In this disease the percentage of sugar increases in the blood (hyperglycemia) so that sugar overflows into the urine (glycosuria). The hyperglycemia is associated with a breakdown of the first stage in the metabolism of sugar, as revealed by the deficient formation of glucose-6-phosphate and the consequent failure of glycogen deposition in the liver and the failure of the respiratory quotient to become increased when carbohydrate food is ingested. The depression in carbohydrate metabolism may be accompanied by an accumulation of ketone substances (acetone, acetoacetic and oxybutyric acids) with resultant acidosis and, later, coma.

### Insulin

Insulin, if administered subcutaneously, intravenously, or intraperitoneally, causes a fall in the sugar content of the blood. Insulin prevents the hyperglycemia due to piquêre, asphyxia and epinephrine. It increases the sugar consumption of the isolated mammalian heart. Insulin also causes glycogen to be deposited in the liver and possibly in the muscles, and raises the respiratory quotient of diabetic animals fed with carbohydrates. It affects the metabolism of fat in diabetic animals and causes the acetone bodies to disappear from the urine.

Insulin also acts as an antagonist to certain pituitary and adrenal hormones. When the percentage of blood sugar falls below the kidney threshold in the diabetic patient, sugar disappears from the urine. If an overdose of insulin is given, the blood sugar falls to a subnormal level, and characteristic symptoms are observed. The level at which these symptoms occur depends not only on the extent but also on the rate of fall. If the blood sugar has been persistently high and is rapidly reduced, hypoglycemic symptoms may appear at a much higher level of blood sugar than when the fall is slower and more gradual. These symptoms are due to the diminished sugar content of the blood, as shown by the fact that they are relieved by the replacement of the sugar by oral or intravenous administration.

Clinical assays conducted on patients with uncomplicated diabetes on certain standard dietary regimens reveal that one insulin unit



promotes the metabolism of approximately 1.5 Gm. of dextrose. The administration of insulin to diabetic dogs and to men with severe diabetes mellitus temporarily restores the impaired ability to oxidize carbohydrate and to store glycogen in the liver. If a suitable dose of insulin is administered at regular intervals to a person suffering from diabetes mellitus, the blood sugar is maintained at a normal level, the urine remains free of sugar and there is less combustion of fat. As a result, ketone bodies do not appear in the urine and diabetic acidosis and coma are prevented.

Properly employed, insulin is also of value in the management of diabetic patients undergoing surgery and of those with complicating infectious diseases. It makes possible freedom from glycosuria and good mental and physical vigor for patients with severe diabetes.

Administration of insulin is indicated in cases of diabetes mellitus which cannot be controlled at a satisfactory level by dietetic treatment. In such cases, the diet should be carefully weighed and of known composition, and insulin administered in such amounts as to prevent glycosuria and excessive hyperglycemia. In some cases the dosage of insulin may be gradually decreased as the body's capacity for utilizing carbohydrate returns toward normal.

There is no positive evidence that treatment with insulin restores the patient's antidiabetic function. In severer cases, evidence is against such an assumption. In the milder cases in which insulin has been used, the evidence is difficult to interpret because dietary regulation and exercise alone may produce improvement.

In diabetes, reliance on the oral administration of the pancreatic preparations thus far available is to be condemned. Pancreatin-U.S.P., a preparation of whole pancreas, while of no value in the treatment of diabetes mellitus, may be of some use after pancreatectomy or in pancreatic disease associated with a lack of or deficient external secretion of the pancreas. It is standardized to convert not less than twenty-five times its weight of potato starch or casein into soluble carbohydrates and proteoses, respectively.

**Overdosage.**—Overdosage of insulin produces serious symptoms which demand immediate treatment. The patient complains of weakness, fatigue and nervousness or tremulousness, followed by profuse sweating, the most characteristic sign of overdosage, and sometimes pallor or flushing. In severe forms there is acute distress with mental disturbances and even unconsciousness. These symptoms are relieved by the administration of some form of soluble carbohydrate, such as orange juice, by mouth or stomach tube, or, if the patient is comatose, by the intravenous injection of 5 to 20 Gm. of pure dextrose in a 5 to 50 per cent sterile solution. Although symptoms of hypoglycemia usually develop gradually, the onset may be sudden. For this reason, ambulant patients should be instructed to carry, for immediate use, soluble carbohydrate in the form of powdered dextrose or an orange. For physicians treating patients with insulin, it is necessary to have adequate supplies of a sterile solution of dextrose at hand. In case of emergency when sterile solution of dextrose is not available, a subcutaneous injection of 0.3 to 0.6 cc. of 1:1,000 solution of epinephrine may be employed, but this must always be followed by carbohydrates by



mouth. The injection of epinephrine must be employed carefully as its action depends on the presence of glycogen, of which there is usually very little in the diabetic organism. Epinephrine should never be employed when the hypoglycemia follows excessive exercise, vomiting or the omission of meals.

Insulin has been used in the treatment of nondiabetic malnutrition with reported increase in appetite and gain in weight. Care is necessary to avoid symptoms of hypoglycemia.

Insulin has been suggested and used rather extensively in psychopathic hospitals to produce hypoglycemic shock in the schizophrenic. It is a dangerous procedure with a relatively high mortality and should be employed only by those who are fully equipped, fully qualified and thoroughly familiar with all aspects of this method of treatment. It is essential to have available at all times suitable solutions of dextrose for interrupting the hypoglycemic state which is thus artificially created.

**Dosage.**—Insulin is administered by injection into the loose subcutaneous tissue of the body, usually 30 minutes before meals. There is no average dose of insulin for diabetics; each case must be studied individually. Except when complications occur insulin is not indicated when a patient has adequate dextrose tolerance to provide him with a diet sufficient for light work. The dose depends upon the amount of dextrose in such a diet which he is unable to metabolize; i.e., the total dextrose minus the dextrose excretion. A convenient formula is: 
$$\frac{\text{Average grams of d-glucose excreted}}{1.5} = \text{suffi-}$$

cient units of insulin to render most patients aglycosuric. In mild diabetes, a single dose of insulin usually is given before breakfast. If glycosuria is not controlled in this way, a smaller dose may be given before supper. When more than one dose is required daily, it is usually better to use one of the long-acting insulin preparations. Less carbohydrate should be given at breakfast than at the other two meals. When the patient becomes aglycosuric the diet may usually be increased. Sufficient insulin should be used to keep the fasting blood sugar normal, but hypoglycemia should be avoided. If patients are not under close observation, half the estimated dose may be used and the dose gradually increased until therapeutic results are obtained. Complications, such as infections, may reduce the dextrose tolerance, thus necessitating an increase of insulin dosage.

In cases of coma or severe acidosis an initial dose of 30 to 60 units may be given (in coma one-half the amount intravenously and one-half subcutaneously) followed at  $\frac{1}{2}$ -hour intervals by doses of 20 units or more subcutaneously. Some physicians administer 1 Gm. of dextrose for each unit of insulin used. The patient should never become hypoglycemic. Examine the urine hourly for dextrose. If urine becomes sugar-free more dextrose must be given. More than 150 units of insulin in 12 hours is occasionally needed. Young children with diabetes of recent onset usually require smaller doses and seldom more than 80 units in the first 12 hours.

In a small number of cases of diabetes mellitus, insulin can be discontinued, particularly with patients who receive it because of an exacerbation caused by complications, and where diabetes is of

recent onset (though perhaps the latter should receive it intermittently as a prophylactic against increasing severity of attacks).

*Dosage of insulin should always be expressed in units rather than in cubic centimeters or minims.* The volume of a dose of insulin containing a certain number of units will vary with the strength of the solution employed. It is advisable to keep the volume per injection at 0.25 to 0.75 cc., choosing the strength of insulin which will give the required number of units within this range.

Insulin injection prepared from zinc insulin crystals, globin insulin injection and protamine zinc insulin are all official in the *U. S. Pharmacopeia*. Unmodified insulin is the preparation of choice in the treatment of diabetes acidosis and coma and when the glucose tolerance is fluctuating rapidly, as in the presence of infection, shock or surgical trauma.

Canadian patents 234,336 and 234,337. U. S. trademark 179,174. Canadian trademark 31,646.

### *Insulin Labeling Regulations*

Regulations concerning the certification of batches of drugs composed wholly or partly of insulin are presented in the 15 Federal Register 7359, Nov. 2, 1950, as amended by 16 F.R. 10157, Oct. 5, 1951, and 17 F.R. 1822, Feb. 29, 1952. Of special interest to the physician are statements on labeling. Each package must contain on the outside wrapper information on the batch mark, strength of the drug in terms of U.S.P. units of insulin per cubic centimeter, expiration date, and the warning "Keep in a cold place: Avoid freezing." The circular or other labeling must contain special information for the guidance of the physician and patient. The outside containers or wrappers must be distinguished by various colors.

Insulin U.S.P. is distinguished by:

**Red**, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

**Green**, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

**Orange**, if it contains 100 U.S.P. Units of insulin in each cubic centimeter.

Narrow (at least 5 but not more than 20 to each inch) **brown** and **white** diagonal stripes, if it contains 500 U.S.P. Units of insulin per cubic centimeter.

If the master lot used was in crystalline form the distinguishing colors may be:

**Red** and **gray**, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

**Green** and **gray**, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.



Protamine zinc insulin is distinguished by:

*Red and white*, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

*Green and white*, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

Globin zinc insulin is distinguished by:

*Red and brown*, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

*Green and brown*, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

Isophane (NPH) insulin is distinguished by:

*Red and blue*, if it contains 40 U.S.P. Units of insulin in each cubic centimeter.

*Green and blue*, if it contains 80 U.S.P. Units of insulin in each cubic centimeter.

**ZINC INSULIN CRYSTALS.**—A crystalline preparation of the active antidiabetic principle of the internal secretion of the islands of Langerhans of the pancreas. The crystals contain a small amount of zinc (not less than 0.45 per cent and not more than 0.9 per cent), which is chemically combined with the active principle. Each milligram of the crystals is equivalent to not less than 22 units of insulin. The product is marketed in the form of a solution for injection.

Marketed solutions of zinc insulin crystals are water clear and contain from 1.4 to 1.8 per cent (W/V) of glycerin for isotonicity, 0.1 to 0.25 per cent (W/V) of phenol or tricresol as a preservative and sufficient 0.01 *N* hydrochloric acid to yield a pH of 2.5 to 3.5. The biologic activity of the solution is expressed in U.S.P. Insulin Units per cubic centimeter. Solutions of zinc insulin crystals are stable, provided the storage temperature does not exceed room temperature.

**Actions and Uses.**—Zinc insulin crystals are used in the form of injectable solutions in the treatment of diabetes mellitus which is not controlled by diet. Ordinarily, crystalline preparations are interchangeable with amorphous preparations. However, because of their purity, solutions of zinc insulin crystals minimize the allergic reactions which sometimes occur with amorphous insulin. Crystalline solutions are therefore indicated for patients who may be expected to exhibit such reactions.

**Dosage.**—The potency of solutions of zinc insulin crystals is measured in terms of standard units of insulin. Like solutions of regular amorphous insulin, solutions of zinc insulin crystals are usually best administered subcutaneously 15 to 30 minutes before a meal. The time and number of doses and the amount of solution



must be determined by the needs of the individual patient, each one requiring accurate dietary regulation and meticulous clinical study

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Insulin Made From Zinc Insulin Crystals:** 10 cc. vials. Aqueous solutions containing 40 units or 80 units in each cubic centimeter. Preserved with 0.1 per cent of phenol.

### *Long-Acting Insulin Preparations*

Several preparations of insulin combined with globin or protamine are used to prolong the blood sugar lowering action of the hormone. These vary in their duration of action from 15 to 72 hours and characteristically possess a slower onset of action than insulin. Since hypoglycemic episodes are most likely to occur during the period of peak effect, the time intervals for administration of the longer-acting preparations should be adjusted to avoid possible occurrence of nocturnal hypoglycemia. When asleep, the patient is not aware of the characteristic symptoms and therefore would not institute prompt countermeasures.

The chart which follows summarizes the characteristic actions of the various forms of long-acting insulin and is presented as a guide. It should be noted, however, that patients may vary considerably in their reactions, each requiring meticulous clinical study to determine the onset, peak and duration of action of the preparation used.

	<i>Soluble Unmodified and Crystalline Zinc Insulin</i>	<i>Globin Insulin</i>	<i>Isophane Insulin</i>	<i>Protamine Zinc Insulin</i>
Onset	1 hr.	1 to 2 hrs.	1 to 2 hrs.	4 to 6 hrs.
Peak Action	2 to 3 hrs.	6 to 12 hrs.	10 to 20 hrs.	16 to 24 hrs.
Duration	6 to 8 hrs.	18 to 24 hrs.	20 to 32 hrs.	24 to 36 hrs. or longer

**GLOBIN ZINC INSULIN.**—A preparation of insulin modified by the addition of zinc chloride and globin. The globin used is obtained from globin hydrochloride prepared from beef blood and conforms to the regulations of the Food and Drug Administration concerning certification of batches of drugs composed wholly or partly of insulin.

*Globin zinc insulin differs in its action from that of insulin and protamine zinc insulin both in time of onset and duration.*

**Physical Properties.**—Globin zinc insulin injection is an almost colorless liquid, substantially free from turbidity and insoluble matter. Globin zinc insulin injection contains from 1.3 to 1.7 per cent (w/v) of glycerin and either 0.15 to 0.2 per cent (w/v) of cresol or 0.2 to 0.26 per cent (w/v) of phenol. It contains 0.25

to 0.35 mg. of zinc for each 100 U.S.P. Units. It also contains 3.6 to 4 mg. of globin (calculated as six times the nitrogen content of the globin) for each 100 U.S.P. Insulin Units.

**Actions and Uses.**—The effects of globin insulin with zinc are essentially the same as those of insulin except that the action is intermediate between that following regular insulin and protamine zinc insulin. The period of greatest effect extends from the eighth to the sixteenth hour after injection; it almost disappears at the end of 24 hours. This agent may be used for the treatment of diabetic patients in whom regulation of diet alone is incapable of providing adequate control and in some patients to replace, wholly or partly, ordinary insulin. It is indicated for patients who require more than one daily injection of unmodified insulin and for those whose sugar level cannot be controlled by other forms of insulin or who exhibit sensitivity to protamine. Its injection also produces fewer local reactions. It is not recommended for the treatment of diabetic coma and should never be administered intravenously. Globin insulin with zinc is stable but nevertheless bears on the label an expiration date for usage.

**Dosage.**—For general principles underlying the administration of this form of insulin see the general statement on insulin. Globin zinc insulin must be administered only by deep subcutaneous injection, not intramuscularly or intravenously. Dosage must be determined by a study of the patient. The initial dose may be about two-thirds to three-fourths of the total daily dose of regular insulin. This may be increased slowly as needed. If the patient has been receiving protamine zinc insulin, the globin insulin dosage on the first day should not exceed one-half the total dose of all insulin (regular, protamine zinc) received on the previous day. On the next day the dose may be increased to two-thirds of the previous total insulin dosage and then slowly adjusted.

The dosage forms listed below are identical to Globin Zinc Insulin Injection-U.S.P.

#### BURROUGHS WELLCOME & COMPANY, INC.

**Globin Insulin with Zinc:** 10 cc. vials. A sterile solution in hydrochloric acid of 40 or 80 U.S.P. Insulin Units in each cubic centimeter. Preserved with 0.25 per cent phenol.

U. S. patent 2,161,198.

#### E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Globin Zinc Insulin:** 10 cc. vials. A sterile solution in hydrochloric acid of 40 or 80 U.S.P. Insulin Units in each cubic centimeter. Preserved with 0.25 per cent phenol.

**ISOPHANE INSULIN.**—NPH Iletin (LILLY).—NPH Insulin.—“NPH insulin is a preparation of crystals containing insulin, protamine, and zinc, suspended in a buffered medium. Zinc-insulin crystals are used in such quantity that each cubic centimeter of the preparation, when the precipitate therein is brought into uniform suspension, contains either 40 or 80 U.S.P. Units of insulin. Prota-



mine is used in such quantity that the preparation contains not less than 0.3 milligram nor more than 0.6 milligram for each 100 U.S.P. Units of insulin; but the quantity is not less than that of the isophane ratio . . . and does not exceed that of the isophane ratio by more than 10 per cent. The preparation contains, for each 100 U.S.P. Units of insulin, not less than 0.016 milligram and not more than 0.04 milligram zinc and not more than 0.85 milligram nitrogen. Disodium phosphate (calculated as  $\text{Na}_2\text{HPO}_4$ ) is used in a quantity not less than 0.15 per cent and not more than 0.25 per cent (w/v). The pH of the finished preparation is not less than 7.1 and not more than 7.4. The preparation also contains either (a) and not less than 1.4 and not more than 1.8 per cent (w/v) glycerin and not less than 0.15 and not more than 0.17 per cent (w/v) meta-cresol and not less than 0.06 and not more than 0.07 per cent (w/v) phenol, or (b) not less than 0.42 and not more than 0.45 per cent (w/v) sodium chloride and not less than 0.7 and not more than 0.9 per cent (w/v) glycerin and not less than 0.18 and not more than 0.22 per cent (w/v) meta-cresol. The protamine used is prepared from the sperm of mature testes of fish belonging to the genera *Oncorhynchus* Suckley, *Salmo* Linné, or *Trutta* Jordan and Evermann (Fam. *Salmonidae*).” Regulations promulgated September 28, 1950 by the Administrator, Federal Security Agency: Certification of Batches of Drugs Composed Wholly or Partly of Insulin [15 Fed. Reg. 7363 (Nov. 2, 1950)].

Isophane insulin conforms to the regulations of the Food and Drug Administration concerning certification of batches of drugs composed wholly or partly of insulin.

Isophane insulin injection has about one-half to one-fifth the protamine and about one-sixth to one-twelfth the zinc content of protamine zinc insulin injection.

**Actions and Uses.**—Essentially, isophane insulin is a modification of protamine zinc insulin, but it differs in being crystalline rather than amorphous in character. The pharmacologic action of isophane insulin is similar to that of the other insulins. Its blood sugar lowering action places it in an intermediate position between globin insulin and protamine zinc insulin. The onset of action for isophane insulin begins usually 2 hours after subcutaneous injection, whereas 6 to 8 hours are required for protamine zinc insulin. Its peak effect occurs 10 to 20 hours after administration, and its duration of action is 28 to 30 hours.

Isophane insulin may be mixed with regular insulin. Loss of quick action of regular insulin is less with isophane insulin than with similar mixtures of protamine zinc insulin, because isophane insulin contains less available protamine. Used in conjunction with regulation of diet and exercise, this form of insulin is of value in control of severe and labile diabetes. It is not recommended for children below 5 years of age or for patients who require quick-acting insulin.

**Dosage.**—See the monograph on protamine zinc insulin.

**Warning.**—If administered after breakfast, danger of nocturnal hypoglycemia exists.



## ELI LILLY &amp; COMPANY

NPH Iletin: 10 cc. vials. 40 units or 80 units in each cubic centimeter. Preserved with 0.15 per cent *m*-cresol and 0.06 per cent phenol.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

NPH Insulin: 10 cc. vials. 40 units or 80 units in each cubic centimeter. Preserved with 0.15 per cent *m*-cresol and 0.06 per cent phenol.

**PROTAMINE ZINC INSULIN.**—Protamine Zinc and Iletin (LILLY).—A preparation of insulin modified by the addition of zinc chloride and protamine. The protamine is prepared from the sperm or from the mature testes of fish belonging to the genera *Oncorhynchus* Suckley, *Salmo* Linné, or *Trutta* Jordan and Evermann (Fam. *Salmonidae*), and conforms to the regulations of the Food and Drug Administration concerning certification of batches of drugs composed wholly or partly of insulin.

*Protamine zinc insulin differs in its action from that of insulin and globin zinc insulin both in time of onset and duration. To secure accuracy of dosage, preparations must be brought into uniform suspension by careful shaking before use.*

**Physical Properties.**—Protamine zinc insulin injection is a white suspension and is freed of large particles when agitated moderately.

**Actions and Uses.**—The effects of protamine zinc insulin are the same as those of insulin (see general statement on insulin), except that unmodified insulin lowers blood sugar maximally in 2 to 3 hours, whereas the action of protamine zinc insulin in lowering blood sugar is prolonged and the agent is most effective 12 to 24 hours after administration.

Protamine zinc insulin may be used in any patient in whom regulation of diet is incapable of removing the cardinal objective symptoms of diabetes mellitus, and may replace, wholly or partly, the use of unmodified insulin. Unmodified insulin alone, protamine zinc insulin alone or both preparations give best results in different cases.

Because of the prolonged action of protamine zinc insulin, it is useful chiefly in cases where unmodified insulin does not provide control unless administered several times daily or where it is unable to provide adequate control unaccompanied by frequent hypoglycemic reactions, ketosis or pronounced fluctuations in blood sugar levels and when insulins of intermediate duration of action are also unsatisfactory. The use of protamine zinc insulin in patients in diabetic coma, in diabetes complicated by infection, or in the event of surgical operations is not recommended.

**Dosage.**—For the general principles underlying the administration of protamine zinc insulin see the general statement on insulin.

Protamine zinc insulin is to be injected *only subcutaneously*. In most cases its administration is not required more than once a day.

The initial dose should be from about two-thirds to the same number of units that would be needed with unmodified insulin. Owing to the slow absorption and consequent delayed action of protamine zinc insulin, glycosuria may follow. Hence on the first few days when protamine zinc insulin is being used, it may be advantageous to administer a separate dose of unmodified insulin. It is usually possible to discontinue the use of unmodified insulin after the first or second day, although in some instances the administration of both preparations must be continued indefinitely.

Protamine zinc insulin is administered in the morning (from one-half to one and one-half hours before breakfast). Because protamine zinc insulin lowers the blood sugar level over a prolonged period, diet must be adjusted, and a redistribution of food among individual meals is usually desirable. The carbohydrate content of the meal following the injection of protamine zinc insulin may have to be limited to avoid hyperglycemia. The carbohydrate not included in this meal is divided between the other meals of the day, often including a night feeding, in such a manner as to prevent hypoglycemia at times when the dose of protamine zinc insulin is exerting its greatest effect.

Symptoms of hypoglycemic reactions following administration of protamine zinc insulin are similar to but may be less obvious than those following injection of unmodified insulin, and may consist merely of fatigue unwarranted by the activities of the patient. Hypoglycemic reaction occasioned by protamine zinc insulin may be prolonged, and despite its having been treated, may repeat itself owing to the continuing effect of the dose administered. It is therefore advisable to use both a soluble and a more slowly digestible carbohydrate in treating such reactions, for example, corn syrup with bread or bread with honey. Alternatively, and even though the patient may appear to be restored to normal through use of a soluble carbohydrate food such as orange juice, it is advisable to provide additional carbohydrate such as soda biscuits and milk after 1 or 2 hours. In severe reactions, it may be desirable to inject intravenously 15 to 20 Gm. of dextrose in sterile solution, giving food later.

The dosage forms listed below are identical to Protamine Zinc Insulin Injection-U.S.P.

#### ELI LILLY & COMPANY

**Suspension Protamine Zinc and Iletin:** 10 cc. vials. A buffered suspension containing 40 or 80 U.S.P. Insulin Units in each cubic centimeter.

Iletin is registered under U. S. trademark 171,971.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Suspension Protamine Zinc Insulin:** 10 cc. vials. A buffered suspension containing 40 or 80 U.S.P. Insulin Units in each cubic centimeter. Preserved with 0.25 per cent phenol.

U. S. patents 2,076,082, 2,143,590 and 2,143,591.



E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

Suspension Protamine Zinc Insulin: 10 cc. vials. A buffered suspension containing 40 or 80 U.S.P. Insulin Units in each cubic centimeter.

## PITUITARY GLAND

**Anterior Lobe.**—The anterior lobe is apparently not necessary for life but is required for normal growth and sexual development. After extirpation of the gland, in addition to arrested growth and failure of sexual development, atrophy of the thyroid and adrenal cortex occurs. Hypophysectomized animals have low blood sugar, low glycogen stores, insulin sensitivity, decreased metabolic rate and a general loss of spontaneous activity. Such animals respond feebly to various stresses, including infections.

Three types of cells are recognized in the anterior lobe: (1) chromophobe cells which stain poorly, show no granules and comprise about 50 per cent of the total; (2) acidophilic cells (alpha cells) containing acidophilic granules after staining, constituting about 35 per cent of the total mass and (3) basophilic cells (beta cells).

Although a large number of active substances in extracts and preparations of the anterior lobe have been described, many are probably not distinct compounds. How many distinct hormones are secreted by the gland is unknown, but at least seven extracts having highly specific action have been prepared in a relatively pure state. These are: (1) A growth factor which influences the development of the body; (2) a factor (follicle-stimulating hormone, FSH) which stimulates the growth and maturation of the ovarian follicle, which in turn brings on the changes characteristic of the first half of the menstrual cycle; (3) a factor (luteinizing hormone, LH) which causes luteinization of the ovarian follicles; (4) a factor (thyrotropic hormone) which is necessary for normal thyroid development and function and which, if present in excess, produces hyperplasia of the thyroid with hyperthyroidism in both the rat and the guinea pig; (5) a factor which produces lactation in mammals and possibly plays a part in mammary gland proliferation, also inducing a secretion of crop milk in pigeons; (6) a diabetogenic principle, held by some investigators to be the growth factor, which decreases the hypoglycemic response to insulin and which damages indirectly the cells of the islets of Langerhans, thus producing the diabetic syndrome; (7) the adrenocorticotrophic hormone (corticotropin, ACTH), a factor which stimulates the adrenal cortex.

The gonadotropic hormones are also necessary for sexual development in the male, although the roles of FSH and LH are not clear. The growth hormone is believed to be derived from the acidophilic cells of the gland. The cellular source of the other factors is uncertain.



While several of these factors are in use in clinical studies, only corticotropin (ACTH) and gonadotropin are commercially available at the present time.

The Council believes that extensive clinical trial has failed to establish the value of desiccated pituitary preparations for oral administration whether these are prepared from the anterior or from the posterior lobe.

**Posterior Lobe.**—Extraction of the posterior lobe of the pituitary gland yields substances which stimulate smooth muscle, especially that of the blood vessels and the uterus. The strength of this effect varies under different conditions; relaxation may even occur, or a sequence of relaxation and contraction. Thus, intravenous or intramuscular injection of preparations of the posterior lobe is sometimes followed by an increase in blood pressure which is maintained over a considerable period. Subsequent doses have a similar effect unless given too soon after the first injection, when a fall in pressure may occur. The increase in pressure is due to contraction of the smooth muscle of the vessels. Because of variation in the effect on muscle, in some persons the increase in blood pressure following injection of pituitary preparations may be very slight or instead of an increase, a decrease of the blood pressure may occur.

The heart is not stimulated in any case and may be depressed by toxic doses, either through vagus response to high blood pressure, by direct action on the heart muscle or through impairment of its nutrition because of constriction of the coronary vessels. The tone of the intestinal tract may be increased by direct action on the muscular coat. The administration of extracts usually retards the secretion of urine during the first hour and a half or more following injection. There is some experimental evidence that the absorption of water from the gastro-intestinal tract is delayed, thereby lessening the water available for secretion. However, the anti-diuretic action may be due to increased reabsorption of water from the kidney tubules into the blood associated with changes in electrolyte balance. The bladder musculature is stimulated especially when it has been previously in an atonic condition. Posterior pituitary extract does not increase the formation of milk, but may cause a temporary acceleration of the output. The extract of the posterior lobe causes contraction of the uterus by direct stimulation of the muscle. The intensity of the action varies with the species, the stage in the estrus or menstrual cycle, the presence or absence of pregnancy and the stage of pregnancy.

Intramuscular injections of solutions prepared from the posterior lobe are employed against uterine atony and to check postpartum and other uterine hemorrhage. They should not be given during the first stage of labor because, if the cervix is not fully dilated, energetic contractions may cause rupture of the uterus or extensive laceration of the soft tissue. Most authorities also advise against the use of pituitary preparations in the second stage of labor.

Pituitary solutions may be useful in intestinal paresis, whether it follows abdominal operations or occurs as a complication in infectious diseases.

The extracts are also extensively used in diabetes insipidus, in

which they reduce greatly the volume of urine excreted. For this purpose they are injected once or twice daily.

The extracts should always be injected hypodermically or intramuscularly although some activity appears when they are applied to the nasal mucous membrane. The extract of the posterior lobe of the pituitary gland has been fractionated: One product (oxytocin) acts on the uterus and a second product (vasopressin) acts on the blood vessels, intestine and urinary secretion. Vasopressin also has an oxytotic action on the human uterus but its other effects make it less desirable as an oxytotic agent.

The *U. S. Pharmacopeia* includes posterior pituitary injection, containing both oxytotic and vasopressor factors, and oxytocin injection, containing chiefly the oxytotic factor. The usual intramuscular dose of the former is 0.3 to 0.5 cc. and of the latter, 0.5 cc. The *U. S. Pharmacopeia* also includes vasopressin injection, the actions of which are identical to solutions of vasopressin tannate, except that the tannate form is never administered intravenously.

**CORTICOTROPIN.—Acthar (ARMOUR).—**Corticotropin is a preparation having adrenocorticotropic activity derived from the anterior pituitary of certain domesticated animals. It is prepared by acid acetone extraction of animal pituitaries and purified by fractional precipitation. It is assayed biologically by measurement of the adrenal ascorbic acid response in hypophysectomized rats. An International Standard has been established by the World Health Organization. The U.S.P. unit is identical with the International Unit. Each is defined as representing the specific adrenocorticotropic activity of 1 mg. of the International Standard.

**Actions and Uses.**—The adrenocorticotropic hormone of the anterior pituitary gland stimulates the adrenal cortex to secrete its entire spectrum of hormones. Experimental evidence suggests that Compound F (hydrocortisone) is the chief component in the adrenocortical secretion although considerable quantities of cortisone and corticosterone are elaborated. Hormonal effect can be exerted only if a functioning adrenal cortex is present. Corticotropin is rapidly utilized in the body; its effect rarely exceeds 6 hours. This necessitates repeated intramuscular administration of the drug or use of a slowly absorbed preparation. Corticotropin also may be administered intravenously by slow continuous drip over 8 hours; its effect usually persists for approximately 24 hours. The physiologic and metabolic effects of the hormone are due to the adrenal corticosteroids elaborated and are, in general, similar to those described for cortisone acetate. Because of its rapid absorption and utilization these effects appear more promptly than with parenteral or oral administration of cortisone acetate. The prompt fall of the circulating eosinophil count when therapeutic doses of corticotropin are given is the basis for the Thorn test of adrenocortical response. The drug is of value in the same disease conditions for which cortisone acetate is used except that it is not effective for the treatment of Addison's disease.

In general, long term administration of either corticotropin or



cortisone acetate induces similar undesired hormonal effects. However, hypertension and virilism are more likely with the use of corticotropin, while cortisone acetate may elicit involution or partial atrophy of the adrenal cortex. A period of depressed adrenocortical function follows sudden cessation of corticotropin administration, but may be avoided by gradual reduction both of the dosage and the number of doses given.

The potent metabolic effects of corticotropin require frequent check on the patient's weight, blood pressure and electrolyte balance. A high potassium, low sodium intake is advisable if protracted treatment or a large dose of corticotropin is necessary.

With intravenous administration of corticotropin certain additional precautions are necessary. Patients known to be sensitive to animal extracts should have suitable intracutaneous tests with the brand of corticotropin to be used. If such tests are positive, it is preferable to use corticotropin from another animal source. Potassium intake of 2 to 5 Gm. daily should be assured, otherwise the reactions are the same as observed with intramuscular injection. Therapeutic response, however, is more prompt and in some instances patients refractory to intramuscular injection have responded following intravenous administration.

Corticotropin is contraindicated for long-term treatment in hypertension, diabetes mellitus, mental disturbances, chronic nephritis, congestive heart failure, Cushing's syndrome and hirsutism. It has been reported that allergic sensitivity to corticotropin may develop in a small percentage of patients; the reactions have varied from anaphylactoid shock to giant urticaria.

**Dosage.**—The average adult dose of corticotropin is 40 to 50 U.S.P. units daily, administered intramuscularly in four divided doses. If the desired clinical effect is not obtained, the dosage may be cautiously and gradually increased to a total of 100 U.S.P. units daily. Maintenance dosage should be at the lowest level required to continue clinical improvement.

Intravenous administration by continuous drip apparently is more efficient in eliciting response and therefore requires lower dosage schedules. For intravenous use, 5 to 20 U.S.P. units are dissolved in 500 cc. of 5 per cent glucose in water or in 500 cc. of normal saline solution and administered slowly over an 8-hour period. *Caution: Normal saline should not be used as the diluent if the patient is on a low salt regimen.*

#### THE ARMOUR LABORATORIES

**Lyophilized Acthar (Pork):** Vials containing the equivalent of 10, 15, 25 and 40 provisional U.S.P. units of corticotropin.

#### THE UPJOHN COMPANY

**Lyophilized Corticotropin (Sheep):** Vials containing the equivalent of 25 and 40 provisional U.S.P. units of corticotropin.

#### THE WILSON LABORATORIES

**Solution Corticotropin:** 5 cc. vials. A solution containing the



equivalent of 40 U.S.P. units of corticotropin in each cubic centimeter. Preserved with 0.5 per cent phenol.

**PURIFIED CORTICOTROPIN.**—Purified corticotropin is prepared by the adsorption of corticotropin from a dilute acetic acid solution on oxycellulose and the subsequent elution of the adsorbed material with dilute hydrochloric acid. This method yields a product having 10 to 40 times the adrenocorticotropic activity of an equivalent weight of corticotropin.

Purified corticotropin is assayed biologically by measurement of the adrenal ascorbic acid depletion response in hypophysectomized rats. Comparison is made to the Provisional U.S.P. Corticotropin Reference Standard, the injections being made intravenously as with corticotropin. When injected subcutaneously or intramuscularly, however, purified corticotropin produces a greater clinical effect unit for unit than does corticotropin; thus 1 U.S.P. of purified corticotropin produces a clinical effect attained by 3 or 4 units of corticotropin. But when administered intravenously, one U.S.P. unit of purified corticotropin, as measured by rat assay, produces the same range of clinical response as one unit of corticotropin. The exact reason for this discrepancy in response is unknown. It has been hypothesized that the cruder corticotropin carries with it some factors which permit more rapid enzymatic destruction in muscle or skin. These factors are thought to be absent, or present in lesser quantity, in purified corticotropin. For the convenience of physicians, the potency of purified corticotropin is expressed in terms of clinical activity equivalent to a specified number of U.S.P. units of corticotropin, so that treatment may be changed from corticotropin to purified corticotropin without gross adjustments in dosage requirement.

**Actions and Uses.**—See the monograph on corticotropin. Purified corticotropin has the advantage of causing fewer sensitization reactions than corticotropin. When administered in the form of a gel containing 150 mg. of gelatin per cubic centimeter, the total daily dosage of purified corticotropin may be given in one dose and adrenocorticotropic activity persists for approximately 18 to 24 hours.

**Dosage.**—As the dosage of purified corticotropin is expressed in clinical equivalents of U.S.P. units of corticotropin, it should be employed in the same dosage as corticotropin when administered intramuscularly or subcutaneously. If administered by the intravenous route, three clinical equivalents of purified corticotropin must be administered to obtain the same range of clinical activity as obtained with each U.S.P. unit of corticotropin. As the gel, the entire daily dosage may be administered intramuscularly or subcutaneously at 24 hour intervals.

#### THE WILSON LABORATORIES

**Purified Corticotropin-Gel:** 5 cc. vials. When administered intramuscularly or subcutaneously, each cubic centimeter is clinically equivalent to 20, 40, 80 or 100 U.S.P. units of corticotropin. Preserved with 0.5 per cent phenol.

**VASOPRESSIN TANNATE.**—*Pitressin Tannate* (PARKE, DAVIS).— $\beta$ -Hypophamine tannate.—Vasopressin tannate is the water-insoluble tannate of the pressor principle of the posterior lobe of the pituitary body of healthy domesticated animals used for food by man.

Vasopressin tannate is assayed biologically.

**Actions and Uses.**—Vasopressin tannate raises blood pressure, increases the muscular activity of the bladder and intestinal tract and exerts an antidiuretic effect in diabetes insipidus. (See the general statement on the pituitary gland.) The action of vasopressin tannate is more prolonged than that of vasopressin, and it is used, therefore, when prolonged action is desired, particularly for the treatment of patients suffering from diabetes insipidus.

**Dosage.**—0.3 to 1 cc. (1.5 to 5 pressor units) of a solution is given by intramuscular injection at intervals of 36 to 48 hours. *Never administer vasopressin tannate intravenously.*

PARKE, DAVIS & COMPANY

**Solution Pitressin Tannate in Oil:** 1 cc. ampuls. A suspension in peanut oil containing vasopressin tannate equivalent in activity to 5 pressor units of vasopressin in each cubic centimeter.

U. S. patent 2,399,742. U. S. trademark 254,507.

## PLACENTA

### Gonadotropic Substances

There are three types of biologic substances which stimulate the gonads of either sex. The fundamental physiologic gonadotropic hormone of the normal animal body is produced by the anterior pituitary. The chemical nature of this material is unknown, but it is established that there are two distinct components in the pituitary gonadotropic hormone.

The serum of the pregnant mare contains a gonadotropic substance whose action is similar to that of the preparations made from the anterior lobe. This substance is susceptible of refinement to a point where very little inert protein accompanies the active gonadotropic substance. It is probable that only one active compound is involved. An international unit of this substance has been defined by the special committee of the League of Nations, by comparison with a dry powder preparation supposed to be of stable potency. No preparation of this material has been accepted by the Council.

The urine of pregnant women contains a gonadotropic substance distinct from that in the serum of the pregnant mare. The latter substance does not pass out into the mare's urine in appreciable amounts, whereas abundant amounts of the hormone called chorionic gonadotropic substance appear in the urine of pregnant women.

Injection of pregnancy urine, or certain extracts thereof, in rodents induces follicular growth and corpus luteum formation.



When the gonadotropic activity of pregnancy urine was first demonstrated by Zondek, it was believed that the anterior pituitary secreted the substance responsible. On the basis of its effect in the rat, mouse and rabbit, the concept was advanced that this gonadotropin consisted of two hormones—prolan A, the follicle-stimulating hormone and prolan B, the luteinizing hormone. Further experimentation, however, has revealed that this substance is a single entity, that it arises from the placenta rather than from the pituitary and that it differs fundamentally from the gonadotropins of the anterior lobe. This substance is the basis of the Aschheim-Zondek test for pregnancy.

A significant physiologic difference between chorionic gonadotropin and preparations from the anterior pituitary is the inability of the former to stimulate appreciably the ovary of the hypophysectomized rat, the monkey or the human being. Injection of chorionic gonadotropin into primates will not induce follicular growth or corpus luteum formation. On the contrary, reliable investigators have observed definite degenerative changes in the ovaries of women and monkeys treated with this substance. Furthermore, no clear-cut endometrial responses have been observed in primates treated in this manner, which indicates conclusively the inability of this substance to stimulate the growth of normal ovarian structures.

The physiologic action of chorionic gonadotropin is not limited to the female. It also acts on the interstitial cells of the testes, causing them to elaborate the androgenic hormone of the testis, which in turn induces growth of the accessory sex organs. This substance is effective in male monkeys and human beings. Among the reactions induced in the prepuberal monkey is the descent of the testes. In some animals there may be some increase in the size of the seminiferous tubules, but there is little if any effect on the germinal epithelium. Spermatogenesis is maintained by chorionic gonadotropin in recently hypophysectomized rats, but it is not restored after atrophy or induced in normal immature rats.

The therapeutic application of chorionic gonadotropin has covered a wide range. Many of the trials have been unsound or improperly conceived. Its use in the treatment of ovarian disturbance, for example, has no scientific rationale at the present time, although when it was first introduced for the treatment of these dysfunctions the physiologic basis for therapy appeared excellent.

**CHORIONIC GONADOTROPIN.**—Entromone (ENDO).—Follutein (SQUIBB).—The water-soluble gonadotropic substance obtained from the urine of pregnant women by selective precipitation and fractionation procedures. It is a glycoprotein containing about 12 per cent of galactose. This preparation is standardized in international units. One international unit equals 0.1 mg. of a standardized powder (see Council Report, *J.A.M.A.* 113:2,418 [Dec. 30] 1939).

**Physical Properties.**—Chorionic gonadotropin is a relatively pure preparation in which the active material is a glycoprotein soluble in water. It is relatively unstable in aqueous solution and is pre-



pared either as a powder or in glycerin solution to be diluted with saline at time of use.

**Actions and Uses.**—Chorionic gonadotropin is recommended in the treatment of cryptorchism where there are no anatomic lesions causing obstruction of testicular descent. The diagnosis of an anatomic lesion can often be made where this therapy fails. Thus the surgical treatment of cryptorchism may be instituted at an early age when it is found that hormonotherapy cannot induce descent. Excessive therapy may result in pseudo-puberty and possibly other harmful reactions.

The diagnosis of cryptorchism should not include those cases which have been termed pseudocryptorchids, in which the testes are maintained in the inguinal canal as the result of reflex muscular spasm. It will be found that the testes return to the normal scrotal position with gentle handling and warmth.

Chorionic gonadotropin therapy in other disorders, including hypogonadism in the adult, is still considered experimental because of the lack of convincing data. Its value in the treatment of uterine bleeding of functional nature is also as yet unproved, although numerous reports on this therapy have appeared in scientific publications. Considerable disagreement exists regarding the type of bleeding benefited. There is less enthusiasm for this therapy at present than there was several years ago.

**Dosage.**—The usual dose in cryptorchism is 500 to 1,000 international units two to three times a week. Long-continued injections may be dangerous and treatment should not be continued after 8 weeks in the absence of progressive descent. Therapy should be discontinued on the development of signs of precocious maturity.

#### B. F. ASCHER & COMPANY, INC.

**Lyophilized Chorionic Gonadotropin:** 10 cc. vials containing 5,000 I. U. powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. (vial) of sterile distilled water containing 0.5 per cent phenol, makes a solution having a potency of 500 I. U. in each cubic centimeter.

#### COLE CHEMICAL COMPANY

**Chorionic Gonadotropin:** 5,000 I. U. in 10 cc. vials. A powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. (vial) of sterile distilled water preserved with 0.5 per cent chlorobutanol, provides solutions having a potency of 500 I. U. in each cubic centimeter.

#### ENDO PRODUCTS, INC.

**Powder Entromone:** 5,000 I. U. and 10,000 I. U., in 10 cc. vials. A powdered preparation of chorionic gonadotropin, which when diluted with 9 cc. of the accompanying isotonic solution of sodium chloride preserved with 0.4 per cent phenol, provides solutions having a potency of 500 or 1,000 I. U. in each cubic centimeter.

U. S. patent 1,910,298. U. S. trademark 354,550.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Follutein:** 1,000, 5,000 and 10,000 I. U. vials containing a powdered preparation of chorionic gonadotropin which, when diluted with the accompanying 10 cc. of sterile distilled water containing 0.5 per cent phenol, provides a solution having a potency of 100, 500 and 1,000 I. U. per cubic centimeter, respectively.

#### THE UPJOHN COMPANY

**Powder Chorionic Gonadotropin:** 5,000 I. U. in 10 cc. vials. A powdered preparation of chorionic gonadotropin which when diluted with the accompanying 5 cc. (ampul) of injectable water provides a solution having a potency of 1,000 I. U. of chorionic gonadotropin in each cubic centimeter. Preserved with 0.5 per cent of chlorobutanol.

## TESTES

Testosterone, or testicular hormone, has been isolated from testicular tissue. It is secreted by the interstitial cells under the influence of the anterior hypophysis and is responsible for the development and maintenance of the accessory male organs and characteristics. It also produces systemic effects such as nitrogen retention and effects on skin, muscle, bone and organs. Following castration in the male, seminal vesicles, prostate and penis undergo severe atrophy; libido and sexual activity are diminished. Parenteral and oral administration of androgenic preparations will restore these structures and functions to normal; but beneficial effects in castrates or eunuchoids are present only as long as replacement therapy is continued. Testosterone has also been shown to maintain spermatogenesis in the hypophysectomized animal if treatment is begun immediately after the operation; it suppresses sperm formation in the intact adult but permanent suppression has not been found. In adequate doses, this androgen is effective in selected cases of menorrhagia, metrorrhagia and dysmenorrhea, breast engorgement and for the suppression of lactation. For the investigational use of testosterone propionate in cancer of the breast, see the monograph on testosterone propionate.

A spontaneous cessation of hormone release by the testis with aging has been recognized as a rare entity termed male climacteric or menopause. Symptoms are similar to those of the female menopause. In the vast majority of instances, the vague manifestations of a psychoneurosis are incorrectly confused with those of organic testicular disorder. Criteria for laboratory confirmation of the diagnosis of male climacteric are equally confused. At present, such diagnosis probably is not justified without the demonstration of castration levels of urinary gonadotropin, as in the female. Testosterone provides effective replacement therapy only in the true disorder.

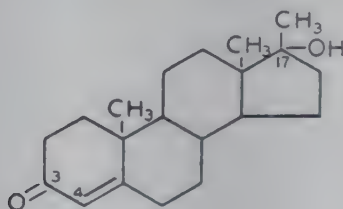
Relief of symptoms due to prostatism following treatment with testosterone has been claimed, but substantial evidence is lacking.



Other claims made by promoters of this substance are **unwarranted** or concern uses which are still experimental.

Testosterone is not excreted in the urine, and should not be confused with the urinary androgens which have relatively little action on mammalian sexual tissue. Commercial testosterone is synthetic, and is usually marketed in the form of testosterone propionate and of methyltestosterone. Testosterone propionate is the most effective available androgen which is suitable for parenteral use; the efficiency of the testosterone is increased because its absorption from the site of injection is delayed by its combination with propionic acid. Methyltestosterone, a synthetic derivative, is much more active than testosterone when given orally, but their physiologic actions are similar. Androgens, like estrogens, are preferably administered orally, unless this route is contraindicated. Testosterone is effective to a limited extent by percutaneous and sublingual administration. Pellet implantation is also occasionally used.

**METHYLTESTOSTERONE-U.S.P.** — 17-Methyltestosterone. — 17-Methyl- $\Delta^4$ -androstene-17( $\alpha$ )-ol-3-one.—The structural formula of methyltestosterone may be represented as follows:



**Physical Properties.**—Methyltestosterone occurs as white or creamy-white crystals or crystalline powder. It is odorless and is stable in air; it is affected by light. It is insoluble in water; it is soluble in alcohol, methanol, ether and other organic solvents and sparingly soluble in vegetable oils.

**Actions and Uses.**—Methyltestosterone may be given orally in the treatment of gonadal failure in the male. Its actions and uses are qualitatively the same as those of testosterone propionate. Methyltestosterone is also useful for the treatment of the female in the control of menorrhagia and metrorrhagia and in postpartum inhibition of lactation or breast engorgement. A unique and rare type of jaundice has been described, which occurs during therapy, and has obstructive and hepatic features.

**Dosage.**—The dosage and duration of methyltestosterone therapy vary considerably, depending upon the condition, its severity, previous androgenic administration and individual variation. It is usually preferable to begin therapy with full doses of 30 to 50 mg. daily in divided dosage. For suppression of breast engorgement 25 to 30 mg. every 4 hours or three times daily for five or six doses should be administered starting at the beginning of lactation, i.e., the third or fourth day after delivery.



**PHYSICIANS' DRUG & SUPPLY COMPANY**

Tablets Methyltestosterone: 10 mg.

**PREMO PHARMACEUTICAL LABORATORIES, INC.**

Tablets Methyltestosterone: 10 mg. and 25 mg.

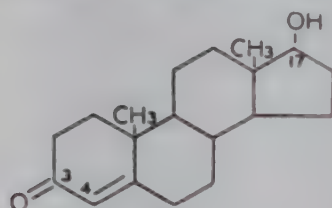
**THE UPJOHN COMPANY**

Tablets Methyltestosterone: 10 mg. and 25 mg.

**WHITE LABORATORIES, INC.**

Tablets Methyltestosterone: 10 mg. and 25 mg.

**TESTOSTERONE-U.S.P.—Androlin (LINCOLN).**—The structural formula of testosterone may be represented as follows:



**Physical Properties.**—Testosterone occurs as white or slightly creamy white crystals or as a crystalline powder. It is odorless and is stable in air. Testosterone is insoluble in water. One gram dissolves in about 6 ml. of dehydrated alcohol, in 2 ml. of chloroform and in about 100 ml. of ether. It is soluble in dioxane and in vegetable oils.

**Actions and Uses.**—Testosterone is responsible for the actions of its derivative, testosterone propionate, and shares its uses. Testosterone in aqueous suspension apparently has a slightly lesser intensity and a slightly greater duration of androgenic action than testosterone propionate.

**Dosage.**—See the monograph on testosterone propionate.

**BIO-INTRASOL LABORATORIES, INC.**

**Aqueous Suspension Testosterone with Procaine Hydrochloride 1%:** 10 cc. vials. A suspension containing 25 or 50 mg. of testosterone in each cubic centimeter. Preserved with 0.01 per cent thimerosal.

**LINCOLN LABORATORIES, INC.**

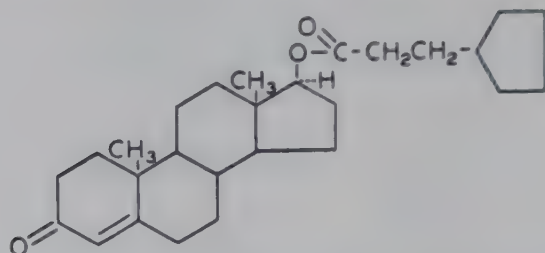
**Aqueous Suspension Androlin:** 10 cc. vials. A suspension containing 25 or 50 mg. of testosterone in each cubic centimeter. Preserved with 0.01 per cent thimerosal.

**METROPOLITAN LABORATORIES, INC.**

**Aqueous Suspension Testosterone with Benzyl Alcohol 2%:** 10 cc. vials. A suspension containing 10, 25, 50 or 100 mg. of testosterone in each cubic centimeter.

**TESTOSTERONE CYCLOPENTYLPROPIONATE.**— $\Delta^4$ -Androstene-

17( $\beta$ )-cyclopentylpropionate-3-one.—The structural formula of testosterone cyclopentylpropionate may be represented as follows:



**Physical Properties.**—Testosterone cyclopentylpropionate is an off-white, odorless, tasteless, crystalline powder. It melts between 98 and 101°. It is freely soluble in alcohol, chloroform and ether, soluble in vegetable oils and slightly soluble in water.

**Actions and Uses.**—The actions and uses of testosterone cyclopentylpropionate are qualitatively the same as those of testosterone propionate, but it possesses the advantage of a more protracted androgenic effect. See the monograph on testosterone propionate.

**Dosage.**—Testosterone cyclopentylpropionate is administered intramuscularly in doses ranging from 10 to 50 mg. at intervals of 7 to 14 days. For induction of pubescence in eunuchoidism, 25 to 50 mg. once weekly may be required for several weeks. In eunuchism, 100 to 150 mg. may be employed at weekly intervals. For relief of constitutional symptoms resulting from deficiency of testicular function, 25 mg. every 2 weeks may be ample. Maintenance dosage must be determined by trial and error for each patient, utilizing the smallest dose and longest time interval between injections consonant with satisfactory control.

Because of the likelihood of virilism, it is advisable not to exceed a monthly dosage of 150 mg. in the treatment of gynecologic conditions. In the treatment of menorrhagia, 25 mg. administered approximately 1 week before the anticipated menses usually will control excessive bleeding. For metrorrhagia, 25 mg. should be administered at approximately weekly intervals, but this dose may be repeated at more frequent intervals if necessary to control bleeding. For suppression of lactation and to lessen breast engorgement, 100 mg. in a single injection is given in the early postpartum period. Experience is lacking for recommendations of dosage for palliation of breast cancer.

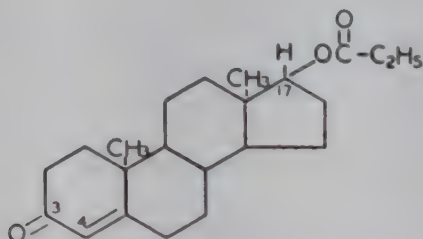
#### THE UPJOHN COMPANY

**Solution Depo-Testosterone Cyclopentylpropionate in Oil:** 10 cc. vials. A solution in cottonseed oil containing 50 mg. or 100 mg. of testosterone cyclopentylpropionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

U. S. trademark 515,760.

**TESTOSTERONE PROPIONATE-U.S.P.** —  $\Delta^4$ -Androstene-17( $\alpha$ )-propionate-3-one.—Testosterone propionate possesses androgenic properties. It may be prepared synthetically from cholesterol as

the starting material or from testosterone isolated from bull testes. The structural formula of testosterone propionate may be represented as follows:



**Physical Properties.**—Testosterone propionate occurs as white or slightly yellow crystals or crystalline powder. It is odorless and is stable in air. It is insoluble in water but freely soluble in alcohol, ether and other organic solvents. It also is soluble in vegetable oils.

**Actions and Uses.**—Testosterone propionate is primarily useful to supply testicular hormone for the treatment of deficiency or absence of this internal secretion of the male. It may therefore be of value in the treatment of prepuberal and postpuberal eunuchoidism or hypogonadism (deficiency states) and after castration or eunuchism due to other causes. In the latter instances treatment is replacement therapy, beneficial only as long as it is continued.

The use of testosterone propionate in eunuchoidism is intended to promote the development of primary and secondary sexual characteristics of patients with organic testicular failure, after the age of 16 or 17 when puberty has not occurred spontaneously and to relieve postpuberal constitutional symptoms attributable to deficient secretion. It is unwise to stimulate full sexual maturity in youths who are psychologically and otherwise physically unprepared for adult life. In eunuchoidism not due to primary testicular hypoplasia, efforts to eliminate secondary etiologic factors should take precedence over the use of androgens.

The use of testosterone in cryptorchism is subject to certain qualifications; for example, hormonal therapy cannot be effective in this condition when there is an anatomic lesion causing obstruction of testicular descent. Testosterone propionate is also useful for the treatment of the female in the control of menorrhagia and metrorrhagia and in postpartum inhibition of lactation or breast engorgement.

For use in castrates and other effects, see general statement on testes.

Testosterone propionate may be tried in the palliation of advanced metastatic carcinoma of the female breast if the patient is considered beyond the help of either surgery or roentgen irradiation. Approximately one-half of the patients so treated experience partial or complete relief of symptoms for periods up to 1 year or more. Occasionally temporary regression of metastatic soft tissue or bone lesions may be observed.

Any patient under treatment with testosterone propionate must be watched carefully for signs of hypercalcemia, edema or acceleration of the disease. Hypercalcemia of severe proportions and ac-



celeration of the disease are contraindications to continuation of testosterone therapy. Edema may be combated with a low sodium diet and the use of ammonium chloride or mercurial diuretics.

Other side effects of testosterone therapy are hirsutism, deepening or hoarseness of the voice, increased libido, enlargement of the clitoris and flushing or acne of the skin.

**Dosage.**—Testosterone propionate is administered intramuscularly in doses ranging from 10 to 50 mg. two to six times weekly, depending on the response obtained. To induce pubescence in eunuchoidism, 25 mg. three times weekly may be employed over a period of several weeks. To relieve constitutional symptoms as little as 10 mg. at similar intervals may be sufficient. The maintenance dose must be determined in each individual case depending on the condition and the effect desired. Priapism is indicative of excessive dosage and an indication for temporary withdrawal of the drug. There has been reported the induction of significant degrees of virilism in women when the amounts of an androgen administered were considerable (350 to 400 mg. testosterone propionate per month). Testosterone propionate has a standard potency of 50 international capon units per milligram and is usually dissolved in oil for intramuscular injection. For the treatment of menorrhagia, 10 mg. triweekly before the onset of the menses is usually sufficient; in metrorrhagia, 25 mg. on alternate days for a total monthly dosage not to exceed 150 mg. is recommended. For suppression of lactation or breast engorgement, from 50 to 75 mg. over a period of 2 or 3 days, starting on the third or fourth day after delivery.

The usual dosage employed for palliation of breast cancer is 150 to 300 mg. of testosterone propionate weekly given in three divided doses; the total duration of therapy is not fully established. At least 2 months of therapy appear to be necessary for a satisfactory subjective response and at least 5 months for any objective response.

#### THE BIO-INTRASOL LABORATORIES, INC.

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 4%:** 10 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 2%:** 10 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Aqueous Suspension Testosterone Propionate with Procaine Hydrochloride 1%:** 10 cc. vials. A suspension in isotonic saline solution containing 25 mg. of testosterone propionate in each cubic centimeter. Preserved with thimerosal 1:10,000.

#### THE BLUE LINE CHEMICAL COMPANY

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%:**

10 cc. vials. A solution in corn oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter.

**CARLO ERBA, INC.**

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 2%:** 10 cc. vials. A solution in peanut oil containing 25 mg. or 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**GOLD LEAF PHARMACAL COMPANY**

**Solution Testosterone Propionate in Oil:** 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 10 mg. of testosterone propionate in each cubic centimeter.

1 cc. ampuls, 10 cc. and 30 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter.

10 cc. and 30 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter.

**METROPOLITAN LABORATORIES, INC.**

**Solution Testosterone Propionate in Oil:** 10 cc. vials. A solution in sesame oil containing 25 mg. or 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**PHYSICIANS' DRUG & SUPPLY COMPANY**

**Solution Testosterone Propionate in Oil:** 10 cc. vials. A solution in peanut oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**PREMO PHARMACEUTICAL LABORATORIES, INC.**

**Solution Testosterone Propionate with 3% Benzyl Alcohol:** 10 cc. vials. A solution in sesame oil containing 25 mg. or 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.1 per cent propylparaben.

**SMITH-DORSEY, DIVISION OF THE WANDER COMPANY**

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%:** 10 cc. vials. A solution in persic oil containing 25 mg. of testosterone propionate in each cubic centimeter.

**TESTAGAR & COMPANY, INC.**

**Solution Testosterone Propionate in Oil:** 10 cc. and 30 cc. vials. A solution in peanut oil containing 25 mg. of testosterone propionate in each cubic centimeter.

10 cc. vials. A solution in peanut oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**S. J. TUTAG & COMPANY**

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%:**

10 cc. vials. A solution in sesame oil containing 25 or 50 mg. of testosterone propionate in each cubic centimeter.

#### THE UPJOHN COMPANY

**Solution Testosterone Propionate in Oil:** 1 cc. and 10 cc. vials. A solution in cottonseed oil containing 25 mg. of testosterone propionate in each cubic centimeter.

10 cc. vials. A solution in cottonseed oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

#### THE VITARINE COMPANY

**Solution Testosterone Propionate in Oil:** 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 10 or 25 mg. of testosterone propionate in each cubic centimeter. Preserved with 0.1 per cent propylparaben.

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 4%:** 1 cc. ampuls and 10 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter.

#### WHITE LABORATORIES, INC.

**Solution Testosterone Propionate in Oil:** 1 cc. ampuls. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter.

10 cc. vials. A solution in sesame oil containing 10 mg. of testosterone propionate in each cubic centimeter. Preserved with phenyl mercuric borate 1:50,000.

10 cc. vials. A solution in sesame oil containing 25 mg. of testosterone propionate in each cubic centimeter.

**Solution Testosterone Propionate in Oil with Benzyl Alcohol 3%:** 6 cc. and 10 cc. vials. A solution in sesame oil containing 50 mg. of testosterone propionate in each cubic centimeter. Preserved with phenyl mercuric borate 1:50,000.



## Immunologic Agents

The first line of defense of the human body, opposed to the ingress of pathogenic parasites, consists of those barriers which mechanically remove or locally destroy such agents of disease. The natural barriers include the skin, mouth, stomach, intestinal tract, nose, nasopharynx, respiratory tract, conjunctivae and genito-urinary tract. Penetration and subsequent multiplication of pathogens in or beneath the natural barriers may result in infection unless the second line of defense, which includes the cellular elements of the blood, the lymph, lymph nodes, the liver and the spleen, mechanically removes and destroys the pathogenic agent.

Resistance to infection which has passed these mechanical barriers is effected by various types of immunity. Immunity connotes the presence, in the animal body, of antibodies, substances which are capable of neutralizing or inhibiting micro-organisms or their metabolic products. The production of antibodies is stimulated when micro-organisms or other foreign substances, designated antigens, elude the mechanical barriers and gain access to the body tissues. In general, an antigen stimulates production of its specific antibody. Protective antibodies are those which interfere with the multiplication and metabolism of pathogenic micro-organisms; other antibodies may cause undesirable reactions, such as anaphylactic shock, when their corresponding antigens are administered.

Innate, or genetic, immunity is the resistance of a given species of animals to various infectious agents; it is particularly important with respect to the communicability of infectious disease from animals to man.

Acquired immunity includes active immunity and passive immunity. Active immunity may be acquired naturally as a result of infection by living pathogens and their metabolic products or it may be induced artificially by inoculation of living, attenuated or dead pathogens or their metabolic products. Agents which induce active immunity include toxins, toxoids and vaccines.

Passive immunity is imparted by transfer of the immunologic properties of the tissue (blood) of an animal with active immunity to another animal of the same or different species. Passive immunity may be naturally (congenitally) acquired or it may be effected artificially by inoculation. Agents which effect passive immunity include antitoxins, antibacterial serums and certain other blood fractions from animals and human beings.

Antibodies formed in the host are less readily excreted than those formed outside the body; therefore, active immunization is preferred to passive immunization because it confers more permanent protection against disease.

Micro-organisms vary in their antigenic (antibody stimulating) property and therefore vaccines prepared from some strains and species are not efficient immunizing agents. There are also differences between human beings, and animals, in their response (i.e., antibody production) to a given vaccine. In acute conditions, it is often undesirable to depend upon this method of active immunization since antibody formation may be too slow to affect the disease. These limitations render passive immunization (use of antibacterial serums, antitoxins, and immune globulins) a more preferable method for the prophylaxis and therapy of certain microbial infections.

Federal regulations control the manufacture and sale of these potent, and in some cases, dangerous products; firms are licensed, under the supervision of the National Institutes of Health of the United States Public Health Service, to import, export or sell these biologic products in interstate commerce. Information regarding tests and standards required by law may be obtained from that agency. The Council considers only licensed biologic products for inclusion in *New and Nonofficial Remedies*.

A number of these products may cause untoward reactions when they are administered as therapeutic or prophylactic agents. Individual sensitivities to animal products, especially horse serum and egg, are primarily responsible for adverse symptoms, and idiosyncrasies toward the products of bacterial metabolism are responsible for others. The Council requires that the labeling and directive literature for all products indicate possible dangerous side reactions.

Although normal human whole blood, serum and plasma may contain antibodies with immunologic properties comparable to those of the above preparations, the low concentrations and instability of the antibodies in those products preclude their utilization for immunization against infectious diseases. Normal blood fractions are described in the chapter on blood derivatives and plasma substitutes.

## IMMUNE SERUMS

Intentional passive immunization against infectious diseases can be effected by parenteral administration of blood serum and its fractions obtained from immune human beings or animals which survived specific natural or artificial infection. The immune substances, antibodies, contained in those fractions either neutralize the metabolic products (toxins) of the micro-organisms or inhibit the growth of the infectious agent.

Toxins are metabolic products excreted by or inherent in some micro-organisms, plants and animals. Examples are the soluble exotoxins excreted by the diphtheria and tetanus bacilli. Antitoxins are prepared for human therapy by immunizing animals against specific toxins.

Immune serums and serum fractions which inhibit the metabolism of pathogenic micro-organisms in the animal body are obtained from human beings and animals following natural or



artificial infection with bacteria and viruses. The antibody titer in immune blood donors may be increased by injection of the specific killed or attenuated micro-organisms. Such serums contain antibodies for all components of the micro-organism (i.e., cell wall, flagella, endotoxins, etc.).

Horses and rabbits are the animals utilized for the artificial production of immune serums. One inoculation with the animal products may sensitize a patient to the blood components of that species, and subsequent inoculations of products from the same animal source may cause serum sickness or anaphylactoid shock. Temporary desensitization can be induced by repeated injections of minute doses or by the use of alternate routes of administration (i.e., subcutaneous) which ensure slow absorption; prevention of the rapid accumulation of antigen in the circulating blood is essential.

The gamma globulin fraction of human blood has been found to contain specific antibodies in the greatest concentration. (See the chapter on blood derivatives and plasma substitutes.)

Because ultraviolet irradiation currently employed for the sterilization of human blood products has not proved as efficient as indicated by previous studies, minimum requirements pertaining to all pooled human serums require a warning statement to the effect that the product may contain the virus of homologous serum hepatitis.

### Animal Source

**ANTI-HEMOPHILUS INFLUENZAE TYPE B SERUM (RABBIT).—**A sterile, refined and concentrated antiserum obtained by immunizing rabbits with *Hemophilus Influenzae* type B; potency is determined by comparison with a standard serum supplied by the National Institutes of Health.

**Actions and Uses.**—Anti-hemophilus influenzae type B serum is used for treatment of influenzal meningitis due to *H. influenzae* type B organisms.

**Dosage.**—After identification of the causative *H. influenzae*, type B, the dosage of serum is determined by estimating the level of spinal fluid dextrose in milligrams per 100 cc. since this varies inversely with the severity of the infection:

SPINAL FLUID DEXTROSE	DOSAGE OF SERUM
Under 15 mg. per 100 cc.	100,000 units
15 to 25 mg. per 100 cc.	75,000 units
25 to 40 mg. per 100 cc.	50,000 units
Over 40 mg. per 100 cc.	25,000 units

The dose is diluted in isotonic sodium chloride solution or Ringer's solution, 10 cc. of solution per kilogram of body weight, and administered intravenously with the speed adjusted so that administration is completed within 2 hours. Adjunctive treatment with aureomycin hydrochloride, streptomycin salts, or sulfadiazine sodium is recommended.



E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Anti-Hemophilus Influenzae Type B Serum (Rabbit):** 25 cc. vials. Each vial contains 25 mg. agglutinin antibody nitrogen equivalent to not less than 25,000 provisional units. Preserved with thimerosal 1:10,000 and 0.2 per cent of phenol.

## Human Source

**HUMAN MEASLES IMMUNE SERUM-N.F.**—Measles Convalescent Serum.—“Human Measles Immune Serum is sterile serum obtained from the blood of a healthy human (*Homo sapiens*) who has survived an attack of measles. Human Measles Immune Serum complies with the requirements of the National Institutes of Health of the United States Public Health Service.” *N.F.*

**Physical Properties.**—Human measles immune serum is a transparent or slightly opalescent liquid of a faint brownish, yellowish or greenish color, nearly odorless or having an odor due to the presence of a preservative. It may have a slight, granular deposit. Human measles immune serum must be free from harmful substances detectable by animal inoculation and must not contain an excessive proportion of preservative (not more than 0.5 per cent of phenol or 0.4 per cent of cresol, if either of these is used).

Human measles immune serum also may be produced as a dry, white or slightly gray powder. The addition of distilled water or other suitable solvent to the dry preparation will produce a liquid which has the characteristics and meets all the requirements described above.

**Actions and Uses.**—Human measles immune serum is administered during the incubation period to prevent or modify the expected attack of measles. To prevent the disease in infants and children of 6 years or under, 10 cc. is given intramuscularly within 5 days after exposure. For children between 7 and 12 years of age, 15 cc. is given and for older children and adults, 20 cc.

The serum may be given intravenously or intramuscularly. Vacuum dried serum should be given only intramuscularly.

Whether the serum is given for prevention or modification depends on the number of days the patient has been exposed. If prevention is desired, however, the dosage may have to be increased to correspond with the length of time which has elapsed since exposure of the patient. If injection is made on the sixth or seventh day after exposure, a high percentage of patients have a modified type of measles which is followed by lasting immunity. It is probable that serum given after the seventh day following the initial exposure has little effect in either preventing or modifying the disease.

**Dosage.**—“Usual dose—Parenteral, therapeutic, 20 cc.; prophylactic, 10 cc.” *N.F.*

JUNIOR LEAGUE BLOOD CENTER OF MILWAUKEE, INC.

**Measles Immune Serum (Human):** 5 cc. and 10 cc. vials.

## MICHAEL REESE RESEARCH FOUNDATION

Human Measles Immune Serum: 5 cc., 7.5 cc. and 20 cc. vials.

**HUMAN PERTUSSIS IMMUNE SERUM.**—The sterile serum prepared from the pooled blood of healthy adult human beings who have received repeated courses of Phase I Pertussis Vaccine. The bloods from which pooled plasma is to be prepared are drawn about one month after a course, or courses, of vaccine, when the donor serum agglutination titer has become greatly elevated, usually 1:640 or higher. The serum may be distributed as a liquid or dried product and as an unmodified serum or one which has been refined and concentrated by an acceptable technic. It complies with the requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—The unmodified serum, whether liquid or dried, may be administered intravenously or intramuscularly for prophylaxis and treatment of "whooping cough." The refined and concentrated product may not be administered intravenously but is intended for both prophylactic and therapeutic use.

**Dosage.**—For treatment, three 20 cc. doses may be injected at 48-hour intervals. A fourth dose may be necessary. Critically ill infants may be given intravenous injections of 60 to 100 cc., the dose may be repeated one or more times.

The foregoing dosage applies only to the unmodified serum. The refined and concentrated serum is several times more potent than the unmodified product. The dosage recommended on the package label should be followed.

## CUTTER LABORATORIES

**Antipertussis Serum (*Hypertussis*) (*Human*):** A highly purified and concentrated globulin prepared from human donors immunized with *H. pertussis* vaccine. Preserved with thimerosal 1:10,000. Each vial contains 2.5 cc., which represents the initial dose. Dose may be repeated as often as indicated by the condition of the patient.

## HYLAND LABORATORIES

**Pertussis Immune Serum (*Human*):** 20 cc. vials of dried, ultra-violet irradiated serum, accompanied by a 20 cc. vial of pyrogen-free diluent.

## JUNIOR LEAGUE BLOOD CENTER OF MILWAUKEE, INC.

**Pertussis Immune Serum (*Human*):** 10 cc. and 20 cc. vials.

## PHILADELPHIA SERUM EXCHANGE, THE CHILDREN'S HOSPITAL OF PHILADELPHIA

**Pertussis Immune Serum (*Human*):** 20 cc. Desi-Pak Vials containing dried ultraviolet irradiated serum.

**HUMAN SCARLET FEVER IMMUNE SERUM-N.F.**—Scarlet Fever Convalescent Serum.—"Human Scarlet Fever Immune Serum is a sterile serum obtained from the blood of a healthy human (*Homo sapiens*) who has survived an attack of scarlet fever. Human Scarlet Fever Immune Serum complies with the requirements of the Na-



tional Institutes of Health of the United States Public Health Service." *N.F.*

**Actions and Uses.**—Human scarlet fever immune serum is of value in transferring passive immunity to a patient exposed to scarlet fever. The evidence as to therapeutic activity is conflicting. It may be used in patients sensitive to horse serum, though the antitoxic content of convalescent serum is low. It is not adequate to meet septic complications.

**Dosage.**—"Usual Dose—Parenteral, therapeutic, 20 cc.; prophylactic, 10 cc." *N.F.*

JUNIOR LEAGUE BLOOD CENTER OF MILWAUKEE, INC.

Scarlet Fever Immune Serum (*Human*): 10 cc. and 20 cc. vials.

MICHAEL REESE RESEARCH FOUNDATION

Human Scarlet Fever Immune Serum: 10 cc. and 20 cc. vials.

**IMMUNE SERUM GLOBULIN (HUMAN)-U.S.P.**—Measles Prophylactic.—"Immune Serum Globulin (Human) is a sterile solution of gamma globulin which contains those antibodies normally present in adult human blood. Its use is limited almost exclusively to prophylaxis against measles. Each lot of the preparation is derived from an original plasma or serum pool which represents at least 500 individuals. Immune Serum Globulin (Human) complies with the requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Physical Properties.**—Immune serum globulin (human) is a transparent or slightly opalescent liquid, either colorless or of a brownish color due to denatured hemoglobin. It is nearly odorless and may develop a slight granular deposit on aging.

**Actions and Uses.**—Immune serum globulin (human) is useful in the prevention and modification of measles. It is equivalent in usefulness to convalescent serum but has the advantage of universal availability. Although it sometimes produces reactions most of these can be avoided by administration of the proper dosage, necessarily modified in accordance with the stage of the incubation period or the prodromal stage of the disease. In the prevention of measles in institutional cases larger doses are required than those given for modification. Prevention is, of course, less desirable than modification except where younger children ill with other diseases are apt to contract measles by exposure to a modified case. Otherwise it is more desirable to permit a child to have mild measles so that immunization occurs than to prevent the disease and leave the child nonimmune to subsequent attacks of the disease. Protection should not be attempted until definite exposure has taken place. Attempts to avoid reactions have led to refinement and concentration of the product and even to its oral administration; the latter cannot be advocated on the basis of present evidence.

**Dosage.**—The amount of immune serum globulin (human) which should be injected depends on the following factors:



1. Whether modification or prevention is desired.
2. The age and general condition of the patient.
3. The intimacy of exposure.

Careful consideration of the available literature is necessary to evaluate these factors and determine an entirely satisfactory dosage, and even then it is not always possible to avoid prevention when modification is desired and vice versa. The following doses are recommended as a general pattern subject to adjustment in accordance with the factors listed above: For prevention, 2 to 10 cc.; for modification, 2 to 5 cc.

#### CUTTER LABORATORIES

Immune Serum Globulin (*Human*): 2 cc. and 10 cc. vials. Preserved with thimerosal 1:10,000.

#### LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Immune Serum Globulin (*Human*): 2 cc. vials. Preserved with thimerosal 1:10,000.

#### PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Immune Serum Globulin (*Human*): 2 cc. and 10 cc. vials. Preserved with thimerosal 1:10,000.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

Immune Serum Globulin (*Human*): 2 cc. and 10 cc. vials. Preserved with thimerosal 1:10,000.

Licensed by Research corporation. U. S. patent 2,390,074.

## TOXOIDS

A toxoid is a toxin modified to reduce its toxicity. Bacterial filtrates, containing toxins and other components of a liquid bacterial culture, can be rendered nontoxic, as measured by appropriate animal tests, without appreciable loss of their antigenic or combining values. Formaldehyde is the agent generally used for the detoxification of toxins.

Toxoids are supplied plain (synonyms: crude, clear, fluid) and as precipitated and adsorbed preparations. Alum,  $\text{Al K}(\text{SO}_4)_2 \cdot 12 \text{H}_2\text{O}$ , is the chemical agent used for the precipitated products, aluminum hydroxide and aluminum phosphate are employed to provide an adsorption surface for toxoids. The precipitated and adsorbed products are more slowly absorbed by the circulating and tissue fluids of the body, and slowly excreted; they therefore provide higher immunizing titers than does a plain toxoid. Nodules are sometimes observed after the injection of these more slowly absorbed products. Rarely, temporary liquefactions occur which should not be incised but allowed to disappear spontaneously. These phenomena are more frequent and appear earlier in the more superficial injections.

Combinations of toxoids from different bacterial species, as well as combinations of toxoids with bacterial vaccines, minimize the

number of inoculations necessary to produce immunization against several infectious agents. It is claimed that such combinations provide more adequate specific immunization with higher antibody titer than the individual components given singly.

### Single Toxoids

**DIPHTHERIA TOXOID, ALUM PRECIPITATED-U.S.P.**—"Alum Precipitated Diphtheria Toxoid is a sterile suspension of diphtheria toxoid precipitated with alum from the solution in which the products of growth of the diphtheria bacillus (*Corynebacterium diphtheriae*) have developed and have been so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retain the property of inducing active immunity. The antigenic value is such that not more than one-half the volume which is to be recommended for the lot under test as the total human immunizing dose produces at least 2 units of antitoxin per cc. of serum in not more than 4 weeks in an aliquot serum-pool from not less than four guinea pigs. Alum Precipitated Diphtheria Toxoid complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Actions and Uses.**—Alum precipitated diphtheria toxoid is used for active immunization against diphtheria. Since some local and general reactions have been observed in adults and in children over eight years of age, an intracutaneous test dose of 0.1 cc. of the toxoid diluted (1:20) with physiologic saline solution should be given to determine sensitivity in these persons. Because of the physical character of the alum precipitated product, absorption is delayed.

**Dosage.**—"Usual dose.—Hypodermic, for active immunization, 1 cc. or 0.5 cc. (whichever is specified on the label) to be repeated once after 4 to 6 weeks." *U.S.P.*

#### NATIONAL DRUG COMPANY

Diphtheria Toxoid (*Alum Precipitated*): 0.5 cc. dose in packages of one 0.5 cc. vial (supplementary dose), one 1 cc. vial (one two-dose immunization), and one 5 cc. vial (five two-dose immunizations). Preserved with thimerosal 1:10,000.

#### PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

Diphtheria Toxoid (*Alum Precipitated*): 5 cc. vials (0.5 cc. dose form); five immunizations. Preserved with thimerosal 1:10,000.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

Diphtheria Toxoid (*Purified, Alum Precipitated*): 1 cc. vials (one two-dose immunization) and 5 cc. vials (five two-dose immunizations).

#### U. S. STANDARD PRODUCTS COMPANY

Aquagen Diphtheria Toxoid (*Alum Precipitated*): 5 cc. (five two-



dose 0.5 cc. immunizations) and 10 cc. (five two-dose 1 cc. immunizations) vials. Preserved with thimerosal 1:10,000.

**Diphtheria Toxoid (*Alum Precipitated Refined*):** 1 cc. and 10 cc. vials in packages of one and of ten 1 cc. vials, and one 10 cc. vial. Preserved with thimerosal 1:10,000.

#### WYETH LABORATORIES, INC.

**Diphtheria Toxoid (*Alum Precipitated Refined*):** 5 cc. and 10 cc. vials. Preserved with 0.01 per cent thimerosal.

#### DIPHTHERIA TOXOID, ALUMINUM HYDROXIDE ADSORBED.—

Aluminum hydroxide adsorbed diphtheria toxoid is a sterile suspension of diphtheria toxoid adsorbed on aluminum hydroxide from the solution in which the products of growth of the diphtheria bacillus (*C. diphtheriae*) have developed and have been so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retain the property of inducing active immunity. The antigenic value is such that not more than one-half the volume which is to be recommended for the lot under test as the total human immunizing dose produces at least 2 units of antitoxin per cubic centimeter of serum in not more than 4 weeks in an aliquot serum-pool from not less than four guinea pigs. Aluminum hydroxide adsorbed diphtheria toxoid complies with the official potency and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on diphtheria toxoid, alum precipitated. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

**Dosage.**—Hypodermic, for active immunization, 0.5 cc. to be repeated once with an interval of 4 to 6 weeks.

#### CUTTER LABORATORIES

**Diphtheria Toxoid, Alhydrox:** 1 cc. vials (one immunization: two 0.5 cc. injections) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

#### DIPHTHERIA TOXOID, ALUMINUM PHOSPHATE ADSORBED.—

Aluminum phosphate adsorbed diphtheria toxoid is a sterile suspension of diphtheria toxoid adsorbed on aluminum phosphate. It is detoxified and standardized for potency as described in the monograph on diphtheria toxoid, aluminum hydroxide adsorbed. Diphtheria toxoid, aluminum phosphate adsorbed, complies with the official potency and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on diphtheria toxoid, alum precipitated. Because of the physical character of the adsorbed product, absorption is delayed.

**Dosage.**—See the monograph on diphtheria toxoid, alum precipitated.

#### PARKE, DAVIS & COMPANY

**Diphtheria Toxoid (*Aluminum Phosphate Adsorbed*):** 1 cc. vials



(one immunization; two 0.5 cc. injections), and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

**TETANUS TOXOID-U.S.P.**—"Tetanus Toxoid is a sterile solution of the products of growth of the tetanus bacillus (*Clostridium tetani*) so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs but retaining the property of inducing active immunity.

"The toxicity of Tetanus Toxoid is so low that five times the greatest volume intended for human injection but not less than 2.0 cc., causes no symptoms of tetanus in a guinea pig within 21 days after its injection into the animal. The antigenic value is such that one-third the volume of plain toxoid which is recommended for the lot under test as the total human immunizing dose protects at least 80 per cent of all the guinea pigs used in the test, not more than six weeks after injection of the toxoid against death from the injection of 10 minimum lethal doses of tetanus test toxin.

"Tetanus Toxoid complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Physical Properties.**—Tetanus toxoid is a brownish-yellow, clear or slightly turbid liquid having a characteristic odor or an odor due to the presence of a preservative. It must not contain an excessive proportion of preservative (not more than 0.5 per cent of phenol or 0.4 per cent of cresol if either of these is used) and must be free from harmful substances detectable by animal inoculation.

**Actions and Uses.**—Tetanus toxoid is used for active immunization against tetanus infection. Active immunization is a desirable procedure in the case of individuals who are subject to a greater than normal hazard of infection.

**Dosage.**—"Usual dose.—Hypodermic, for active immunization. 1 cc. or 0.5 cc. (whichever is specified on the label) to be repeated twice at intervals of three to four weeks." *U.S.P.*

#### CUTTER LABORATORIES

**Tetanus Toxoid:** 1.5 cc. vials (one immunization: three 0.5 cc. injections) and 15 cc. vials (ten immunizations). Preserved with thimerosal 1:10,000.

#### ELI LILLY & COMPANY

**Tetanus Toxoid:** 1.5 cc. (one immunization) and 7.5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

#### U. S. STANDARD PRODUCTS COMPANY

**Aquagen Tetanus Toxoid:** 1.5 cc. (one three-dose immunization), 7.5 cc. (five three-dose immunizations), and 22.5 cc. (fifteen three-dose immunizations) vials. Preserved with thimerosal 1:10,000.

**TETANUS TOXOID, ALUM PRECIPITATED-U.S.P.**—"Alum Precipitated Tetanus Toxoid is a sterile suspension of tetanus toxoid, precipitated with alum from a solution in which the products of

growth of the tetanus bacillus (*Clostridium tetani*) have developed and have been so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs, but retaining the property of inducing active immunity. The antigenic value is such that not more than one-half of the volume, which is to be recommended for the lot under test as the total human immunizing dose, produces at least 2 units of antitoxin per cc. of serum in not more than 6 weeks in an aliquot serum-pool from not less than 4 guinea pigs.

"Alum Precipitated Tetanus Toxoid complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Actions and Uses.**—See the monograph on tetanus toxoid. Because of the physical character of the alum precipitated product, absorption is delayed.

**Dosage.**—"Usual dose.—Hypodermic for active immunization, 1 cc. or 0.5 cc. (whichever is specified on the label) to be repeated once with an interval of four to six weeks." *U.S.P.*

#### ELI LILLY & COMPANY

**Tetanus Toxoid (*Alum Precipitated*):** 1 cc. (one immunization) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

#### NATIONAL DRUG COMPANY

**Tetanus Toxoid (*Alum Precipitated*):** Two 0.5 cc. vials (one immunization), one 5 cc. vial (five immunizations) and one 0.5 cc. vial for supplementary dose. Preserved with thimerosal 1:10,000.

#### PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Tetanus Toxoid (*Alum Precipitated*):** 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

#### SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Tetanus Toxoid (*Purified, Alum Precipitated*):** 1 cc. vials (one two-dose immunization) and 5 cc. vials (five two-dose immunizations). Preserved with thimerosal 1:10,000.

#### E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Tetanus Toxoid (*Alum Precipitated*):** 2 cc. vials for one immunization (two immunizing doses) and 10 cc. vials for five immunizations (ten immunizing doses). Preserved with thimerosal 1:10,000.

#### U. S. STANDARD PRODUCTS COMPANY

**Aquagen Tetanus Toxoid (*Alum Precipitated*):** 1 cc. (one two-dose immunization) and 5 cc. (five two-dose immunizations) vials. Preserved with thimerosal 1:10,000.

#### WYETH LABORATORIES, INC.

**Tetanus Toxoid (*Alum Precipitated Refined*):** 5 cc. and 10 cc. vials. Preserved with 0.01 per cent thimerosal.



**TETANUS TOXOID, ALUMINUM HYDROXIDE ADSORBED.—**

Aluminum hydroxide adsorbed tetanus toxoid is a sterile suspension of tetanus toxoid, adsorbed on aluminum hydroxide from a solution in which the products of growth of the tetanus bacillus (*Clostridium tetani*) have developed and have been so modified by special treatment as to have lost the ability to cause toxic effects in guinea pigs, but retain the property of inducing active immunity. The antigenic value is such that not more than one-half of the volume, which is to be recommended for the lot under test as the total human immunizing dose, produces at least 2 units of antitoxin per cubic centimeter of serum is not more than 6 weeks in an aliquot serum-pool from not less than four guinea pigs.

Aluminum Hydroxide Adsorbed Tetanus Toxoid complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on tetanus toxoid. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

**Dosage.**—Hypodermic, for active immunization, 0.5 cc., to be repeated once with an interval of 4 to 6 weeks.

**CUTTER LABORATORIES**

**Tetanus Toxoid, Alhydrox:** 1 cc. vials (one immunization: two 0.5 cc. injections) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

**Combinations of Toxoids**

**DIPHTHERIA AND TETANUS TOXOIDS-U.S.P.**—"Diphtheria and Tetanus Toxoids is a clear or slightly turbid, yellowish or brownish liquid made by mixing suitable quantities of diphtheria toxoid and tetanus toxoid, each of which possesses adequate potency to permit combining. The toxoids shall be mixed in such proportions as to provide an immunizing dose of each toxoid in the total dosage prescribed on the label. Diphtheria and Tetanus Toxoids complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Actions and Uses.**—Diphtheria and tetanus toxoids is used for active immunization against diphtheria and tetanus.

**Dosage.**—"Usual dose.—Hypodermic; for active immunization 1 cc. or 0.5 cc. (whichever is specified on the label), to be repeated twice at intervals of three to four weeks between injections. Additional doses may be required to secure a negative Schick test." *U.S.P.*

**ELI LILLY & COMPANY**

**Combined Diphtheria-Tetanus Toxoids:** 1.5 cc. vials (one immunization) and 7.5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.



**PARKE, DAVIS & COMPANY**

**Combined Diphtheria-Tetanus Toxoids:** 1.5 cc. vials (one immunization) and 7.5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

**DIPHTHERIA AND TETANUS TOXOIDS, ALUM PRECIPITATED.—U.S.P.**—"Alum Precipitated Diphtheria and Tetanus Toxoids is a turbid, white, slightly gray or slightly pink suspension prepared by mixing suitable quantities of alum precipitated diphtheria toxoid and alum precipitated tetanus toxoid, each of which possesses adequate potency to permit combining. The toxoids shall be mixed in such proportions as to provide an immunizing dose of each toxoid in the total dosage prescribed on the label. Alum Precipitated Diphtheria and Tetanus Toxoids complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Actions and Uses.**—See the monograph on diphtheria and tetanus toxoids. Because of the physical character of the alum precipitated product, absorption is delayed.

**Dosage.**—"Usual dose.—Hypodermic, for active immunization, 1 cc. or 0.5 cc. (whichever is specified on the label) to be repeated once with an interval of four to six weeks. Additional doses may be required to secure a negative Schick test." *U.S.P.*

**ELI LILLY & COMPANY**

**Combined Diphtheria-Tetanus Toxoids (*Alum Precipitated*):** 1 cc. vials (one immunization) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

**NATIONAL DRUG COMPANY**

**Combined Diphtheria and Tetanus Toxoids (*Alum Precipitated*):** Two 0.5 cc. vials (one immunization) and two 2.5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

**PARKE, DAVIS & COMPANY**

**Combined Diphtheria-Tetanus Toxoid (*Alum Precipitated*):** 1 cc. vial. Preserved with benzethonium chloride 1:20,000.

**PITMAN-MOORE COMPANY**

**Combined Diphtheria-Tetanus Toxoid (*Alum Precipitated*):** 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

**E. R. SQUIBB & SONS, DIVISION OF MATHILSON CHEMICAL CORPORATION**

**Combined Diphtheria Toxoid-Tetanus Toxoid (*Alum Precipitated*):** 5 cc. (0.5 cc. dose form) and 10 cc. (1 cc. dose form) vials. Five immunizations each. Preserved with thimerosal 1:10,000.

**WYETH LABORATORIES, INC.**

**Combined Diphtheria-Tetanus Toxoid (*Alum Precipitated*):** 1 cc. and 10 cc. vials in packages of two 1 cc. vials and of one 10 cc. vial. Preserved with 0.01 per cent thimerosal.

**DIPHTHERIA AND TETANUS TOXOIDS, ALUMINUM HYDROXIDE ADSORBED.**—Aluminum hydroxide adsorbed diphtheria and tetanus toxoids is a turbid, white or slightly gray suspension prepared by mixing suitable quantities of aluminum hydroxide adsorbed diphtheria toxoid and aluminum hydroxide adsorbed tetanus toxoid, each of which possesses adequate potency to permit combining. The toxoids shall be mixed in such proportions as to provide an immunizing dose of each toxoid in the total dosage prescribed on the label. Aluminum hydroxide adsorbed diphtheria and tetanus toxoids complies with the requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on diphtheria and tetanus toxoids. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

**Dosage.**—Hypodermic, for active immunization, 0.5 cc. to be repeated once after an interval of 4 to 6 weeks.

#### CUTTER LABORATORIES

**Diphtheria and Tetanus Toxoids Alhydrox:** 1 cc. vials (one immunization: two 0.5 cc. injections) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.

## VACCINES

Vaccines are suspensions of either attenuated or killed micro-organisms which are administered hypodermically for the prevention or treatment of infectious diseases. The use of vaccines provides a method for active immunization. See the general statement on immunologic agents.

Bacterial vaccines also are utilized for their pyrogenic (fever-producing) properties in certain noninfectious diseases.

Vaccines are prepared from bacterial, viral and rickettsial strains of micro-organisms.

Viral and rickettsial vaccines contain, in addition to the micro-organisms, the components of artificially infected tissues (e.g., animal brain tissue and eggs) which are required for the production of those products; inoculation with such foreign proteins may produce dangerous side actions.

Bacterial vaccines are suspensions of micro-organisms which usually have been washed free of the components of the culture medium to reduce the danger of reactions to the antigens it may contain. Newer methods of bacterial vaccine processing provide for the incorporation of the "whole culture" (bacteria, metabolic products and culture medium) in the final product; synthetic culture media, containing hydrolyzed proteins which are less antigenic than are the parent substances, are employed for the production of whole culture vaccines.

**INFLUENZA VIRUS VACCINE, POLYVALENT.**—Influenza Virus Vaccine, polyvalent, is a sterile suspension of formaldehyde-killed



influenza viruses, types A, A prime and B. The vaccine contains types A, A prime and B viruses recovered from the extraembryonic fluids—preferably from the allantoic fluid only—of chick embryos infected with these viruses. The A, A prime and B components are serologically different. Since present knowledge is inadequate with respect to the strains required to provide a vaccine having complete antigenic coverage, the vaccine contains only those strains of the viruses designated by the National Institutes of Health. The product complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—Influenza virus vaccine, polyvalent, is used prophylactically for active immunization against the component strains of influenza viruses. Subcutaneous administration of the vaccine stimulates production of antibodies which appear in the serum approximately a week after injection, reach maximum titers during the second week, remain constant for approximately a month and then gradually decline. The duration of protection following vaccination is still under discussion, because resistance to infection varies widely among individuals. Since the vaccine is prepared with so few strains of the two serologic types of virus, it will not protect against all strains. Administration of the vaccine to individuals with established infections with these viruses is not rational and may lead to increased symptoms.

The vaccine may cause toxic symptoms, particularly in children, because of the high concentration of the inactivated viruses. The vaccine should not be used in persons sensitive to material derived from chick or egg protein.

**Dosage.**—Hypodermically, for prophylactic active immunization, a single dose: 1 cc. for adults, 0.5 cc. or less for children under 12 years of age. A second injection may be indicated in epidemics of influenza virus infections.

#### LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

**Influenza Virus Vaccine, Polyvalent:** 1 cc. vials (one immunization) and 10 cc. vials (ten immunizations). Preserved with thimerosal 1:10,000.

#### ELI LILLY & COMPANY

**Influenza Virus Vaccine, Polyvalent:** 1 cc. and 5 cc. vials. Preserved with thimerosal 1:10,000.

#### THE NATIONAL DRUG COMPANY

**Influenza Virus Vaccine, Polyvalent:** 1 cc. and 5 cc. vials. Preserved with thimerosal 1:10,000.

#### PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Influenza Virus Vaccine, Polyvalent:** 1 cc. vials (one immunization) and 5 cc. vials (five immunizations). Preserved with thimerosal 1:10,000.



SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Influenza Virus Vaccine, Polyvalent, Protamine Concentrated and Refined:** 1 cc. and 10 cc. vials. Preserved with thimerosal 1:10,000. U. S. patent 2,445,301.

**PERTUSSIS VACCINE-U.S.P.**—Whooping cough vaccine.—“Pertussis Vaccine is a sterile suspension in isotonic sodium chloride solution or other suitable diluent of killed pertussis bacilli (*Hemophilus pertussis*) of a strain or strains selected for high antigenic efficiency. . . . Pertussis Vaccine complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service.” *U.S.P.*

**Actions and Uses.**—Well-controlled field studies indicate that pertussis vaccine possesses sufficient antigenic value to afford considerable protection against whooping cough. Its effect in lowering the death rate is even more striking than its effect in preventing attacks of the disease, since cases do occur in spite of previous injection of vaccine. Such cases are usually less severe.

Encephalopathic symptoms occasionally occur with whooping cough and, more rarely, with the use of the prophylactic vaccine. Such severe symptoms of the central nervous system have included convulsions and lethargy. They may be followed by mental or physical manifestations, sometimes permanent, or even by death.

**Dosage.**—The usual immunizing dose is 1.5 cc. (12 units, N.I.H.) administered hypodermically in three divided doses of 0.5 cc. each. The interval for injection is 3 or 4 weeks.

#### CUTTER LABORATORIES

**Pertussis Vaccine:** 1.5 cc. (one immunization: three 0.5 cc. injections), 7.5 cc. (five immunizations) and 15 cc. vials (ten immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

#### ELI LILLY & COMPANY

**Pertussis Vaccine:** 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

#### THE NATIONAL DRUG COMPANY

**Pertussis Vaccine:** 1.5 cc. (one immunization: three 0.5 cc. injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

#### PARKE, DAVIS & COMPANY

**Pertussis Vaccine (Immunizing Sauer):** 1.5 cc. (one immunization) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with 0.01 per cent merthiolate.

#### PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Pertussis Vaccine:** 20 cc. vials (five immunizations: three injec-

tions of 1 cc., 1.5 cc. and 1.5 cc.). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

#### SHERMAN LABORATORIES

**Pertussis Vaccine:** 12.5 cc. vials (three immunizations) and 20 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

#### E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Pertussis Vaccine:** 3 cc. (one immunization) and 15 cc. (five immunizations) vials. Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

#### U. S. STANDARD PRODUCTS COMPANY

**Pertussis Vaccine:** 7.5 cc. (five immunizations) and 22.5 cc. vials (fifteen immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

#### WYETH LABORATORIES, INC.

**Pertussis Vaccine:** 1.5 cc. (one immunization: three 0.5 cc. injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 0.01 per cent.

**PERTUSSIS VACCINE, ALUM PRECIPITATED-U.S.P.**—"Alum Precipitated Pertussis Vaccine is a sterile suspension in a suitable diluent of killed pertussis bacilli (*Hemophilus pertussis*) of a strain or strains selected for high antigenic efficiency and precipitated with alum and resuspended. . . . Alum Precipitated Pertussis Vaccine complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Physical Properties.**—Pertussis vaccine, alum precipitated, is a turbid, whitish liquid. It is essentially odorless. It must be free from harmful substances detectable by animal inoculation and must not contain an excessive proportion of preservative.

**Actions and Uses.**—See the monograph on pertussis vaccine. Because of the physical character of the alum precipitated product, absorption is delayed.

**Dosage.**—The usual hypodermic dose, for active immunization, is 1.5 cc. (12 units, N.I.H.), divided into not less than three individual injections with intervals of 4 to 6 weeks between injections. It is desirable to give a booster dose (0.5 cc.) 1 year after primary immunization and again at school age.

#### THE NATIONAL DRUG COMPANY

**Pertussis Vaccine (Alum Precipitated):** One 0.5 cc. vial (supplementary dose). Preserved with thimerosal 1:10,000. For use as a booster dose to maintain a high protective level.

**Pertussis Vaccine (Alum Precipitated):** 7.5 cc. vials (five im-



munizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Pertussis Vaccine, Alum Precipitated:** 5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:7,500.

**PERTUSSIS VACCINE, ALUMINUM HYDROXIDE ADSORBED.**—Aluminum hydroxide adsorbed pertussis vaccine is a sterile suspension in a suitable diluent of killed pertussis bacilli (*Hemophilus pertussis*) of a strain or strains selected for high antigenic efficiency and adsorbed on aluminum hydroxide. Aluminum hydroxide adsorbed pertussis vaccine complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on pertussis vaccine. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

**Dosage.**—For active immunization, a total of 1.5 cc. (12 units, N.I.H.) is administered hypodermically, divided into not less than three individual injections, with intervals of 4 to 6 weeks between injections.

CUTTER LABORATORIES

**Pertussis Vaccine, Aluminum Hydroxide Adsorbed (Alhydrox):** 7.5 cc. vials (five immunizations: three 0.5 cc. injections for each). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

## COMBINATIONS OF VACCINES AND TOXOIDS

These combinations of active immunizing agents are advantageous in reducing the number of immunization procedures required for immunity against several infectious diseases and in providing a synergistic effect which enhances and increases production of antibodies for each component of the product.

There is some evidence that it is advisable not to perform routine elective immunization with these preparations (or their components) in the summer and early fall, when the incidence of anterior poliomyelitis is high (*J.A.M.A.* 144:259 [Sept. 16], 1950).

**DIPHTHERIA TOXOID AND PERTUSSIS VACCINE COMBINED. U.S.P.**—**Diptussis (CUTTER).**—"Diphtheria Toxoid and Pertussis Vaccine Combined is a sterile mixture of Diphtheria Toxoid and Pertussis Vaccine combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Diphtheria Toxoid and Pertussis Vaccine Combined complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Physical Properties.**—Diphtheria toxoid and pertussis vaccine



combined is a more or less turbid, whitish liquid. It is nearly odorless. It must be free from harmful substances detectable by animal inoculation and must not contain an excessive proportion of preservative.

**Actions and Uses.**—Employed in the simultaneous immunization against diphtheria and whooping cough.

**Dosage.**—"Usual dose—Hypodermic, for active immunization, not less than 3 repeated injections representing the U.S.P. dosage of diphtheria toxoid and of pertussis vaccine." *U.S.P.*

#### CUTTER LABORATORIES

**Diptussis:** 1.5 cc. (one immunization: three 0.5 cc. injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

**DIPHTHERIA TOXOID AND PERTUSSIS VACCINE COMBINED, ALUM PRECIPITATED.**—Alum precipitated diphtheria toxoid and pertussis vaccine combined is a sterile mixture of diphtheria toxoid and pertussis vaccine precipitated with alum and combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Alum precipitated diphtheria toxoid and pertussis vaccine combined complies with the official potency tests and the requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on diphtheria toxoid and pertussis vaccine combined. Because of the physical character of the alum precipitated product, absorption is delayed.

**Dosage.**—Hypodermic, for active immunization, not less than three repeated injections representing the U.S.P. dosage for diphtheria toxoid alum precipitated and for pertussis vaccine alum precipitated.

#### THE NATIONAL DRUG COMPANY

**Diphtheria Toxoid, Alum Precipitated and Pertussis Vaccine Combined:** Three 0.5 cc. vials (one immunization) and three 2.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria toxoid. Preserved with thimerosal 1:10,000.

#### PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Diphtheria Toxoid, Alum Precipitated and Pertussis Vaccine Combined:** 4.5 cc. vials (three immunizations: three 0.5 cc. injections). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria toxoid. Preserved with thimerosal 1:10,000.

**DIPHTHERIA TOXOID AND PERTUSSIS VACCINE COMBINED, ALUMINUM HYDROXIDE ADSORBED.**—**Diptussis, Alhydrox (CUTTER).**—Aluminum hydroxide adsorbed diphtheria toxoid and pertussis vaccine combined is a sterile mixture of diphtheria toxoid and pertussis vaccine, adsorbed on aluminum hydroxide and combined in such proportion as to yield a mixture containing an

immunizing dose of each in the total dosage prescribed on the label. Aluminum hydroxide adsorbed diphtheria toxoid and pertussis vaccine combined complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on diphtheria toxoid and pertussis vaccine combined. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

**Dosage.**—Hypodermic, for active immunization, not less than three repeated injections representing the U.S.P. dosage for diphtheria toxoid, aluminum hydroxide adsorbed and for pertussis vaccine, aluminum hydroxide adsorbed.

#### CUTTER LABORATORIES

**Diptussis, Alhydrox:** 1.5 cc. (one immunization: three 0.5 injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria toxoid. Preserved with thimerosal 1:10,000.

**DIPHTHERIA AND TETANUS TOXOIDS WITH PERTUSSIS VACCINE, COMBINED.**—**Dip-Pert-Tet (CUTTER).**—Diphtheria and tetanus toxoids with pertussis vaccine is a sterile mixture of diphtheria toxoid, tetanus toxoid and pertussis vaccine combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Combined diphtheria and tetanus toxoids with pertussis vaccine complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—Employed in the simultaneous active immunization of susceptible persons against diphtheria, tetanus and whooping cough.

**Dosage.**—Hypodermic, for active immunization, not less than three divided doses, administered at intervals of 3 or 4 weeks, the total being at least the U.S.P. immunizing doses of diphtheria toxoid, tetanus toxoid and pertussis vaccine.

#### CUTTER LABORATORIES

**Dip-Pert-Tet:** 1.5 cc. (one immunization: three 0.5 cc. injections), 7.5 cc. (five immunizations) and 22.5 cc. vials (fifteen immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.

#### ELI LILLY & COMPANY

**Diphtheria and Tetanus Toxoids and Pertussis Vaccine Combined (Fluid):** 1.5 cc. vials (one immunization) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.



E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Combined:** 1.5 cc. (one immunization: three 0.5 cc. injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.

U. S. STANDARD PRODUCTS COMPANY

**Diphtheria and Tetanus Toxoids with Pertussis Vaccine, Combined:** 1.5 cc. (one three-dose immunization), 7.5 cc. (five three-dose immunizations) and 22.5 cc. (fifteen three-dose immunizations) vials. Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.

**DIPHTHERIA AND TETANUS TOXOIDS WITH PERTUSSIS VACCINE COMBINED, ALUM PRECIPITATED.**—**Infagen** (PITMAN-MOORE).—**Trinavac** (SHARP & DOHME).—Combined alum precipitated diphtheria and tetanus toxoids with pertussis vaccine is a sterile mixture of diphtheria toxoid, tetanus toxoid and pertussis vaccine precipitated with alum and combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Alum precipitated diphtheria and tetanus toxoids combined with pertussis vaccine complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on diphtheria and tetanus toxoids with pertussis vaccine combined. Because of the physical character of the alum precipitated product, absorption is delayed.

**Dosage.**—Hypodermic, for active immunization, not less than three divided doses, administered at intervals of 3 to 4 weeks, the total being at least the U.S.P. immunizing doses of diphtheria toxoid alum precipitated, of tetanus toxoid alum precipitated and of pertussis vaccine alum precipitated.

THE NATIONAL DRUG COMPANY

**Diphtheria and Tetanus Toxoids, Alum Precipitated, and Pertussis Vaccine Combined:** Three 0.5 cc. vials (one immunization), three 2.5 cc. vials and one 7.5 cc. vial (five immunizations). One complete immunizing treatment of three 0.5 cc. injections contains two human doses each of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

PITMAN-MOORE COMPANY, DIVISION OF ALLIED LABORATORIES, INC.

**Infagen:** 7.5 cc. vials (five immunizations: three 0.5 cc. injections). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.



SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Trinavac, Alum Precipitated:** One 1.5 cc. vial (one three-dose immunization) and one 7.5 cc. vial (five three-dose immunizations). One three-dose immunization provides a complete immunizing course of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Diphtheria and Tetanus Toxoids Alum Precipitated and Pertussis Vaccine Combined:** 1.5 cc. (one three-dose immunization) and 7.5 cc. vials (five three-dose immunizations). One three-dose immunization provides a complete immunizing course of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

U. S. STANDARD PRODUCTS COMPANY

**Aquagen Diphtheria and Tetanus Toxoids and Pertussis Vaccine Combined, Alum Precipitated:** 1.5 cc. (one three-dose immunization) and 7.5 cc. (five three-dose immunizations) vials. One three-dose immunization provides a complete immunizing course of diphtheria and tetanus toxoids and 12 units of pertussis vaccine. Preserved with thimerosal 1:10,000.

**DIPHTHERIA AND TETANUS TOXOIDS WITH PERTUSSIS VACCINE COMBINED, ALUMINUM HYDROXIDE ADSORBED.**—**Dip-Pert-Tet, Alhydrox (CUTTER).**—Combined aluminum hydroxide adsorbed diphtheria and tetanus toxoids with pertussis vaccine is a sterile mixture of diphtheria toxoid, tetanus toxoid and pertussis vaccine adsorbed on aluminum hydroxide and combined in such proportion as to yield a mixture containing an immunizing dose of each in the total dosage prescribed on the label. Combined aluminum hydroxide adsorbed diphtheria and tetanus toxoids with pertussis vaccine complies with the official potency tests and other requirements of the National Institutes of Health of the United States Public Health Service.

**Actions and Uses.**—See the monograph on diphtheria and tetanus toxoids with pertussis vaccine combined. Because of the physical character of the aluminum hydroxide adsorbed product, absorption is delayed.

**Dosage.**—Hypodermic, for active immunization, not less than three injections administered at intervals of 3 to 4 weeks, the total being at least the dosage of diphtheria toxoid, aluminum hydroxide adsorbed, of tetanus toxoid, aluminum hydroxide adsorbed and of pertussis vaccine, aluminum hydroxide adsorbed.

CUTTER LABORATORIES

**Dip-Pert-Tet, Alhydrox:** 1.5 cc. (one immunization: three 0.5 cc. injections) and 7.5 cc. vials (five immunizations). Total immunizing dose contains 12 units of pertussis vaccine with diphtheria and tetanus toxoids. Preserved with thimerosal 1:10,000.

## AGENTS FOR CUTANEOUS IMMUNITY TESTS

In the armamentarium of preventive medicine, tests for susceptibility to infectious diseases are of great value. Mass immunization programs which prevent epidemics are often based on evidence that a population is susceptible to a given infection.

Modern medicine relies less on tests for susceptibility than formerly was the case; the physician prefers "routine elective" immunization instead when specific immune agents are available.

The tuberculin, diphtheria toxin and scarlet fever streptococcus toxin (Dick test) are agents for testing susceptibility to specific micro-organisms.

A positive tuberculin test, irrespective of the testing method, merely indicates the presence of allergy or hypersensitivity to tuberculin and that the individual is infected or has been infected with tubercle bacilli. A negative tuberculin reaction to the strongest concentration used in testing definitely indicates the absence of tuberculin allergy but does not eliminate the possibility of tuberculous infection in individuals whose skin has become anergic (without allergic reactivity). In rare instances, convalescence from acute infectious disease, anesthesia, early tuberculosis, senility, severe malnutrition and various other conditions may interfere with the test and a false negative tuberculin reaction may be obtained. Tuberculin was formerly used in the therapy of tuberculosis but in recent years they have been superseded by antibiotics and other chemotherapeutic agents.

Differential diagnoses can be made by employing certain immunologic agents, such as the streptococcus antitoxin in the Schultz-Charlton test, for cutaneous reactions.

### Tests for Susceptibility

**PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN-U.S.P.**—"Purified Protein Derivative of Tuberculin is a sterile, soluble product of the growth of the tubercle bacillus (*Mycobacterium tuberculosis*) prepared in a special liquid medium free from protein. Purified Protein Derivative of Tuberculin complies with the official potency test and other requirements of the National Institutes of Health of the United States Public Health Service." *U.S.P.*

**Actions, Uses and Dosage.**—Purified protein derivative of tuberculin is used for the diagnosis of tuberculosis by intracutaneous injection (Mantoux test). A positive local reaction merely indicates that the patient has been infected with tuberculosis at some time, not necessarily that he has clinical tuberculosis at the time of the test. It indicates, however, complete study of the patient since it is presumptive evidence that tubercle bacilli are, or have been, present.

Standard doses of 0.00002 mg. and 0.0002 mg. of purified protein derivative of tuberculin are used. The second dose should not be used until the first has been found to give a negative reaction.

It is marketed in the form of tablets containing these amounts, with a vial of diluent for making freshly prepared solutions. Best results require that the solutions thus prepared be used immediately even though they are somewhat more stable than old tuberculin.

The reaction is determined after 48 hours. If this is negative after a dose of 0.00002 mg., a second dose of 0.0002 mg. should be injected into the opposite arm. If, after 48 hours, no reaction appears, a dose of 0.002 may be injected, but in routine testing of presumably nontuberculous children, the test is rarely carried this far. The reaction consists in a zone of redness at the point of injection, usually with a papule, which reaches its height in 48 hours.

The subcutaneous injection for diagnosis or treatment of tuberculosis, even for nonpulmonary infections, has been largely abandoned as it is capable of harm.

**PARKE, DAVIS & COMPANY**

**Tablets Tuberculin, Purified Protein Derivative (*First Strength*):** Packages containing 2 vials (5 tests each) and 1 cc. vial of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc. vial of diluent.

**Tablets Tuberculin, Purified Protein Derivative (*Second Strength*):** Packages containing 2 vials (5 tests each) and 1 cc. vial of sterile diluent; and packages containing 10 tablets (100 tests) with 10 cc vial of diluent.

**Tablets Tuberculin, Purified Protein Derivative (*First and Second Strength*):** Sufficient for 20 tests each of first and second strength. Packages for individual testing containing 2 vials, 1 tablet each of first strength and 2 vials, 1 tablet each of second strength with a 5 cc. vial of sterile diluent.



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## 18

# Agents Used in Metabolic Disorders

This chapter describes four groups of substances used in the treatment of metabolic disorders: (1) Substances that have a special influence on metabolism, such as thiouracil and derivatives which affect the activity of the thyroid gland; (2) substances that are administered in order that they may be themselves metabolized, such as dextrose, amino acids, salts of calcium, certain compounds of iodine and lipotropic agents; (3) substances used in the replacement of extracellular electrolytes following dehydration and acidosis; and (4) substances used to reduce the concentration of extracellular electrolytes.

Compounds employed only as contrast media for roentgenography or other diagnostic procedures will be found in the chapter on diagnostic aids. Insulin and thyroid preparations, important as metabolic agents, are classified with endocrine substances in the chapter on hormones and synthetic substitutes.

### AMINO ACID AND PROTEIN PREPARATIONS

Amino acid and protein preparations may be conveniently divided into two general classes: (1) Mixtures of those amino acids considered essential to human nutrition and used to combat protein deficiency imposed by severe illness or starvation; (2) individual amino acids that may be used for specific therapeutic purposes.

Preparations in the first class include (a) hydrolysates of protein or sources of protein prepared by various methods of artificial digestion designed to provide adequate amounts of the essential amino acids and (b) mixtures of synthetic amino acids. Preparations in the second class include amino acids such as aminoacetic acid (glycine), formerly used in the treatment of myasthenia gravis, histidine, which has been tried for the treatment of peptic ulcer, and methionine, which has been suggested for the treatment of liver disease. None of these has been established definitely to be of specific therapeutic value in the treatment of the respective conditions mentioned.

Mixtures of the essential amino acids at present are recognized to exert a favorable nutritive effect in peptic ulcer by supplying dietary nitrogen in readily assimilated form when there is serious interference with the intake, digestion or absorption of dietary

protein. There is no evidence that the addition of amino acids to foods will accomplish anything that cannot be accomplished by proper use of proteins as they occur naturally in the diet when there is no such interference.

The amino acids that are now regarded as indispensable for protein synthesis in adult man comprise those which the body is itself unable to synthesize; they are generally listed as follows: phenylalanine, tryptophane, methionine, lysine, leucine, isoleucine, threonine and valine. These eight amino acids or their precursors are usually provided in mixtures intended for protein replacement in human beings.

**Dosage.**—Information is insufficient to permit statement of exact dosage for the amino acids that are prescribed to meet protein needs of the body. Investigations of the daily requirements for the individual amino acids indicate that these range from 0.3 to 5 Gm. Until more is known of human requirements, amino acid preparations must be given in sufficient quantities to provide substantial amounts of every essential constituent. These amounts may be based on the commonly recommended optimum daily intake of total dietary protein: 1 Gm. per kilogram of body weight, or about 70 Gm. daily for the average adult man. This figure is based on the fact that on a mixed diet the average protein intake necessary to maintain nitrogen balance has been found to be about 45 Gm. There are wide variations in individual requirements and in the biologic value of proteins from different sources, but 70 Gm. of protein is ordinarily adequate to meet amino acid requirements.

Amino acid mixtures have appeared on the market in various forms: protein hydrolysates or hydrolytic products of good sources of protein in solution for intravenous injection or in powdered form for oral administration; mixtures of amino acids in tablet form; synthetic amino acids in tablet form; synthetic amino acids combined with vitamins in tablets and elixirs; protein meals for use in tablets or food fortification. Most tablets or elixirs supply amounts insufficient for rational use in human nutrition.

The Council accepts as amino acid mixtures for oral or intravenous administration only hydrolysates of suitable pure proteins (e.g., casein) or good sources of protein (e.g., blood) in which 50 per cent of the total nitrogen present is in the form of alpha amino nitrogen. This minimum degree of hydrolysis is essential to justify the designation of such products as hydrolysates and to insure the nonantigenicity of the mixtures used for intravenous injection and those used orally for infants and children who may be allergic to protein of the diet.

For further information see the section in the rules on general provisions and labeling requirements.

### Amino Acid Mixtures

**AMINOPEPTODRATE.**—Caminoids (ARLINGTON).—An enzymatic digest of extracted liver and beef muscle, wheat gluten, soya, yeast, casein and lactalbumin with dextrose, maltose and sucrose, containing amino acids and polypeptides equivalent to 45 per cent



proteins (N x 6.25) and 40 per cent carbohydrates to provide a total of 350 available calories per 100 Gm.

**Actions and Uses.**—Aminopectodrate is used to supplement the diet in conditions in which especially high protein intake is indicated and it is not feasible to accomplish this by use of ordinary foods. See the monograph on protein hydrolysates.

**Dosage.**—Aminopectodrate provides the average adult daily protein requirement when administered in daily doses of 1 Gm. per kilogram of body weight. It is administered orally in either hot or cold liquids as suited to the patient.

ARLINGTON CHEMICAL COMPANY, DIVISION OF U. S. VITAMIN CORPORATION

**Caminoids:** 170.1 Gm., 453.6 Gm., 2.27 Kg. and 4.54 Kg. containers. One tablespoonful (9 Gm.) contains 4 Gm. of protein as partial hydrolysate.

**PLASMA HYDROLYSATE.**—Travamin (BAXTER).—An artificial digest of protein derived from bovine blood plasma prepared by a method of hydrolysis sufficient to provide more than half of the total nitrogen present in the form of alpha amino nitrogen. When modified either by partial removal or restoration of the constituent amino acid precursors, such products are designated as "Modified Plasma Hydrolysate."

**Actions, Uses and Dosage.**—See the monograph on protein hydrolysates.

BAXTER LABORATORIES, INC.

**Solution Travamin 5%:** 500 cc. and 1 liter bottles. A solution containing 50 mg. of enzymatic hydrolysate of bovine plasma in each cubic centimeter. Fifty per cent of the total nitrogen is present as alpha amino nitrogen.

**Solution Travamin 5% with Dextrose 5%:** 150 cc., 500 cc. and 1 liter bottles. A solution containing 50 mg. of enzymatic hydrolysate of bovine plasma and 50 mg. of dextrose in each cubic centimeter. Fifty per cent of the total nitrogen is present as alpha amino nitrogen.

U. S. trademark 533,766.

**PROTEIN HYDROLYSATES.**—Amigen (MEAD JOHNSON).—Aminonut (NATIONAL DRUG).—Aminosol (ABBOTT).—Hyprotigen (DON BAXTER).—Parenamine (WINTHROP-STEARNES).—Protolysate (MEAD JOHNSON).—These are broadly defined as artificial digests of protein derived by acid, enzymatic or other hydrolysis of casein, lactalbumin, fibrin or other suitable proteins that supply the approximate nutritive equivalent of the source protein in the form of its constituent amino acids. They are required to have more than half of the total nitrogen present in the form of alpha amino nitrogen.

**Actions and Uses.**—Parenteral preparations are useful for the maintenance of positive nitrogen balance in conditions where there is interference with ingestion, digestion or absorption of food.



These conditions are most frequently encountered in severe illness and after surgical operations involving the alimentary tract. The usefulness of hydrolysates is limited when the patient is in a sub-caloric state and, for tissue synthesis, their utilization varies directly with the caloric intake. In the acute "catabolic" phase of nitrogen loss in healthy persons who suddenly become ill, it may be extraordinarily difficult to achieve nitrogen balance with the amount of hydrolysate which can be administered. The acute nitrogen loss of brief severe illness has not been shown to be pernicious, and it is debatable whether hydrolysates should be employed under these circumstances. Protein hydrolysates should not be employed as a substitute for food proteins if the latter can be adequately utilized. They are so distasteful when administered by mouth that many adults refuse to take them by this route, but they may be better tolerated if given through a gastric or duodenal tube.

Intravenous injection is contraindicated during acidosis. Injection may produce untoward effects such as nausea, vomiting, hyperpyrexia (after injections have been given for 5 to 7 days), vasodilatation, abdominal pain, convulsions, edema at the site of injection, phlebitis and thrombosis. Care must be exercised to prevent reactions that indicate danger. Many unfavorable reactions have been traced to inadequate care in the cleanliness of equipment and to too rapid administration. Solutions that are cloudy, contain sediment or have been opened for a previous injection must not be used. Unopened solutions should be stored in a cool place.

Protein hydrolysates that are nutritionally adequate may be used orally in the diets of infants allergic to milk when the deficiency cannot be met by other foods. Protein hydrolysates may also supplement the diet in conditions in which a specially high protein intake is indicated when it is not feasible to accomplish this by use of ordinary foods. Any protein hydrolysate product which has been proved effective for this purpose, may also be employed as an adjunct in the management of peptic ulcer or other ulcerative conditions of the gastro-intestinal tract. Supplementing protein in other conditions is not recommended because there is no evidence of need for such supplementation and if the need should occur, it could be met by the use of ordinary foods.

**Dosage.**—See the general statement on amino acid and protein preparations.

#### ABBOTT LABORATORIES

**Solution Aminosol 5%:** 500 cc. and 1,000 cc. Abbo-Liter bottles. A 5 per cent modified fibrin hydrolysate. A solution containing 5 Gm. of protein hydrolysate equivalent to about 20 calories, 39 mg. of potassium ion and less than 30 mg. of sodium ion in each 100 cubic centimeters.

**Solution Aminosol 5% with Dextrose 5%:** 250 cc., 500 cc. and 1,000 cc. Abbo-Liter bottles. A 5 per cent modified fibrin hydrolysate with 5 per cent dextrose. A solution containing 5 Gm. of

protein hydrolysate and 5 Gm. carbohydrate equivalent to about 40 calories, 39 mg. of potassium ion and less than 30 mg. of sodium ion in each 100 cubic centimeters.

**Solution Aminosol 5% with Dextrose 5% and Sodium Chloride 0.3%:** 1,000 cc. Abbo-Liter bottles. A 5 per cent modified fibrin hydrolysate. A solution containing 5 Gm. of protein hydrolysate and 5 Gm. of carbohydrate equivalent to about 40 calories and 39 mg. of potassium ion in each 100 cubic centimeters.

U. S. trademark 414,539.

#### DON BAXTER, INC.

**Solution Hyprotigen 6%:** 500 cc. and 1,000 cc. bottles. An enzymatic hydrolysate of casein containing amino acids and polypeptides. It contains approximately 55 per cent of its total nitrogen as alpha amino nitrogen.

**Solution Hyprotigen 6% with Dextrose 5%:** 500 cc. and 1,000 cc. bottles. An enzymatic hydrolysate of casein containing amino acids and polypeptides with added dextrose. It contains approximately 55 per cent of its total nitrogen as alpha amino nitrogen.

U. S. trademark 434,994.

#### MEAD JOHNSON & COMPANY

**Powder Protolysate:** 454 Gm. containers. A casein hydrolysate prepared by digestion with fish caeca for oral administration.

U. S. trademarks 425,263 and 423,772.

**Solution Amigen 3.33% with Dextrose in Lactated Ringer's Solution (Diluted 1:3):** 250 cc. bottles. Each 100 cc. contains 3.33 Gm. of protein hydrolysate and 3.33 Gm. of dextrose in lactated Ringer's solution (diluted 1:3).

**Solution Amigen 5% with Dextrose 5%:** Bottles of 125 cc., 500 cc. and 1,000 cc. Each 100 cc. contains 5 Gm. of protein hydrolysate and 5 Gm. of dextrose.

**Solution Amigen 10%:** 500 cc. bottles. Each 100 cc. contains 10 Gm. of protein hydrolysate.

U. S. trademarks 381,523, 387,310 and 422,992.

#### THE NATIONAL DRUG COMPANY

**Powder Aminonat (Flavored):** 226.8 Gm. and 454 Gm. packages. A pancreatic digest of lactalbumin containing amino acids and polypeptides equivalent to about 87.5 per cent hydrolyzed protein providing 128 calories per 28.35 Gm. It has 61 per cent of its total nitrogen as amino nitrogen.

U. S. trademark 424,237.

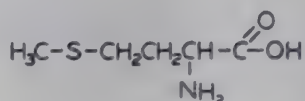
#### WINTHROP-STEARNES, INC.

**Solution Parenamine 6%:** 1,000 cc. bottles. A solution containing 6 Gm. of casein hydrolysate in each 100 cc. The preparation consists essentially of amino acids prepared by acid hydrolysis.

**Solution Parenamine 15%:** 100 cc. bottles. A solution containing 15 Gm. of casein hydrolysate in each 100 cc. A preparation consisting essentially of amino acids which are prepared by acid digestion. Preserved with 0.05 per cent sodium bisulfite.

### Individual Amino Acids

**METHIONINE.** — Meonine (WYETH). — Metione (LOBICA-DEBRUILLE). — DL-Methionine. —  $\alpha$ -Amino- $\gamma$ -methylmercaptobutyric acid.—The structural formula of methionine may be represented as follows:



**Physical Properties.**—Methionine forms white, crystalline platelets or is a powder. It has a faint odor. It is soluble in water, dilute acids and dilute alkalis, very slightly soluble in alcohol and practically insoluble in ether. A 1 per cent aqueous solution of methionine has a pH between 5.6 and 6.1.

**Actions and Uses.**—Methionine is a sulfur-containing amino acid which is considered an indispensable dietary component. It is available in synthetically prepared racemic form that may be administered in sufficient quantity to provide amounts equivalent to the biologically active levo form.

Methionine shares the lipotropic actions and uses of choline and likewise is considered useful as an adjunct in the treatment of liver disease for those patients who cannot take an adequate diet. There is some evidence to suggest that overdosage may be harmful.

**Dosage.**—As a supplement to a high protein diet, 3 to 6 Gm. is usually administered daily in tablet form. In severe cases 10 to 20 Gm. has been used. When oral administration is not feasible, crystalline methionine 5 to 10 Gm. may be given daily by slow intravenous drip as a 3 per cent solution in dextrose injection-U.S.P., or water for injection-U.S.P. that has been further sterilized by autoclaving.

#### ABBOTT LABORATORIES

Tablets Methionine: 0.5 Gm.

#### CHEMO PURO MANUFACTURING CORPORATION

Powder Methionine: Bulk; for manufacturing use.

#### LOBICA-DEBRUILLE, INC.

**Powder Metione (Flavored):** 2 Gm. envelopes. A powder containing in each pliofilm envelope 1.6 Gm. of DL-methionine, 0.16 Gm. of lactose, 0.16 Gm. of sugar and 0.08 Gm. of coffee.

#### TABLEROCK LABORATORIES

Tablets Methionine: 0.5 Gm.



U. S. VITAMIN CORPORATION

Capsules Methionine: 0.5 Gm.

WALKER LABORATORIES, INC.

Capsules Methionine: 0.5 Gm.

WYETH LABORATORIES, INC.

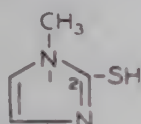
Powder Crystalline Meonine: 50 Gm. bottles.

Tablets Meonine: 0.5 Gm.

U. S. trademark 406,590.

## ANTITHYROID DRUGS

**METHIMAZOLE.**—Tapazole (LILLY).—1-Methyl-2-mercaptoimidazole.—The structural formula for methimazole may be represented as follows:



**Physical Properties.**—Methimazole is a white to buff, crystalline powder which has almost no taste and a very faint odor. It melts between 145 and 148°. One gram dissolves in about 4.5 ml. of water, in about 5 ml. of alcohol, in about 4.4 ml. of chloroform and in about 125 ml. of ether. A 2 per cent solution has a pH between 6.7 and 6.85.

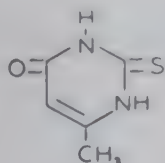
**Actions and Uses.**—Methimazole is similar in indications and uses propylthiouracil, but it is perhaps twenty times as potent and its effect is seen more readily. The side effects are also similar to those of propylthiouracil and have included skin rashes, urticaria, joint pains and agranulocytosis.

**Dosage.**—Initially, 5 to 10 mg. should be given every 8 hours, preferably the larger dose. After the hyperthyroidism is controlled, which may require 30 to 60 days, a maintenance dose of 5 to 10 mg. daily may be expected to keep the disease under control.

ELI LILLY & COMPANY

Tablets Tapazole: 5 mg. and 10 mg.

**METHYLTHIOURACIL.**—Methiacyl (SCHWARZ).—Muracil (ORGANON).—Thimecil (PHYSICIANS' DRUG).—6-Methyl-2-thiouracil.—The structural formula of methylthiouracil may be represented as follows:



**Physical Properties.**—Methylthiouracil is a white, odorless, crystalline powder. Methylthiouracil is very slightly soluble in ether and water, slightly soluble in alcohol and practically insoluble in benzene and chloroform. It melts with decomposition between 326 and 331° (*distinction from propylthiouracil, which melts between 218 and 220°*). It sublimes readily when heated in a platinum dish.

**Actions and Uses.**—Methylthiouracil has actions and uses essentially like those of propylthiouracil. It may prove useful in patients who are unable to tolerate or are refractory to other anti-thyroid drugs. See the monograph on propylthiouracil.

**Dosage.**—0.2 Gm. daily in four divided doses is usually sufficient to control symptoms of hyperthyroidism. The daily dose should not exceed 0.3 Gm. It is recommended that the scheme of administration suggested for propylthiouracil be followed and the same precautions observed.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Methylthiouracil:** Bulk; for manufacturing use.

#### ORGANON, INC.

**Tablets Muracil:** 50 mg.

#### PHYSICIANS' DRUG & SUPPLY COMPANY

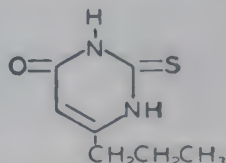
**Tablets Thimecil:** 50 mg.

U. S. patent 505,850.

#### SCHWARZ LABORATORIES, INC.

**Tablets Methiacil:** 50 mg.

**PROPYLTHIOURACIL-U.S.P.** — 6-Propyl-2-thiouracil. — "Propylthiouracil, dried at 105° for 2 hours, contains not less than 98 per cent of  $C_7H_{10}N_2OS$ ." *U.S.P.* The structural formula of propylthiouracil may be represented as follows:



**Physical Properties.**—Propylthiouracil occurs as a white, powdery, crystalline substance. It is starchlike in appearance and to the touch and has a bitter taste. It is very slightly soluble in water. It is sparingly soluble in alcohol and is slightly soluble in chloroform and in ether. It is soluble in ammonia and in alkali hydroxides.

**Actions and Uses.**—Propylthiouracil interferes with the formation of thyroxin by the thyroid gland. It is useful in the treatment of hyperthyroidism.

Since propylthiouracil does not inactivate or interfere with the action of thyroxin already formed and stored in the gland, the effects of propylthiouracil medication do not appear until this store

of thyroxin has been utilized. It may take several days to several weeks for the signs of decreased thyroid activity to become manifest, particularly if the patient has received previous iodine therapy.

Not all patients experience a permanent remission following propylthiouracil therapy, and the duration of treatment necessary to secure permanent relief from hyperthyroidism has not been determined. Propylthiouracil may be used for preoperative treatment, for patients for whom operation is contraindicated and as a substitute for operative procedure.

In the preparation of patients for operation, propylthiouracil reduces the basal metabolic rate to a more nearly normal level than can be brought about by the use of iodine alone. The extreme vascularity and friability of the gland, encountered at operation following the preoperative administration of thiouracil derivatives alone, has been overcome by a longer period of preparation including concomitant administration of iodine for the last 2 or 3 weeks prior to surgery. Propylthiouracil produces sustained effects and is thus not subject to the "escape" from its action that characterizes the use of iodine. Propylthiouracil thus provides more certain and constant control of hyperthyroidism so that preoperative preparation and postoperative course of patients is less difficult than when iodine is used alone.

Propylthiouracil is capable of producing adverse reactions in some patients. The incidence and severity of these reactions are unpredictable but their occurrence is less frequent than following medication with the parent compound, thiouracil. The most severe complication of propylthiouracil therapy is granulocytopenia. If this occurs the drug must be stopped immediately and penicillin administered to prevent the throat infections so common in this condition. Less severe reactions may include leukopenia, drug fever and dermatitis. The drug should be discontinued and appropriate therapy commenced immediately on the detection of signs of any of these complications.

**Dosage.**—In hyperthyroidism an initial dose of 100 mg. every 8 hours is effective in most cases. In some instances, and particularly in severe hyperthyroidism, as much as 600 mg. daily in four to six doses may be required. The compound is rapidly metabolized, and, consequently, effective control requires frequent administration through the 24 hours.

The effective dose of propylthiouracil should be continued until all signs and symptoms of the disease have been brought under control. Adequate maintenance dosage may best be established by symptoms and clinical signs.

#### ABBOTT LABORATORIES

Tablets Propylthiouracil: 25 mg. and 50 mg.

#### LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY

Tablets Propyl Thiouracil: 50 mg.

#### ELI LILLY & COMPANY

Tablets Propylthiouracil: 50 mg.



## PHYSICIANS' DRUG &amp; SUPPLY COMPANY

Tablets Propylthiouracil: 50 mg.

## RAYMER PHARMACAL COMPANY

Tablets Propylthiouracil: 50 mg.

## REXALL DRUG COMPANY

Tablets Propylthiouracil: 50 mg.

## THE UPJOHN COMPANY

Tablets Propylthiouracil: 50 mg.

## CALCIUM COMPOUNDS

Calcium compounds are used therapeutically in overcoming calcium deficiency. The systemic action induced by calcium is dependent on the dosage and the mode of administration, which in turn vary with the calcium salt that is used. Relatively insoluble salts of calcium are administered orally only. Soluble salts may be given either orally or in solution by injection.

Calcium chloride is too irritating for injection other than by the intravenous route and administered orally it produces more gastric irritation than do other soluble compounds. Calcium chloride supplies a large amount of calcium (27 per cent).

The gluconate and levulinate salts, containing 9 and 13 per cent calcium respectively, are relatively nonirritating for subcutaneous or intramuscular injection. However, because muscular necrosis has followed such administration in children, the injection of calcium compounds into the tissues should be restricted to adults.

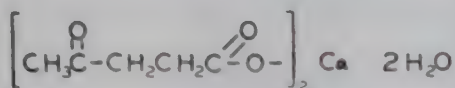
Calcium salts are specific in the treatment of hypocalcemic tetany. Vitamin D or parathyroid hormone may also be indicated according to the etiology involved. In severe tetany, parenteral administration, preferably intravenous, is indicated to bring symptoms under rapid control. Latent tetany or mild symptoms may be controlled by oral medication. When calcium is deficient hydrochloric acid may increase its absorption.

The chloride, lactate or carbonate salts of calcium are all suitable for oral administration in doses corresponding to their calcium content. The administration of large amounts of bicarbonate or persistent vomiting may cause tetany. Tribasic calcium phosphate has been administered orally when phosphorus as well as calcium is deficient, but its use should probably be restricted to less severe forms of calcium deficiency.

Intravenously injected overdoses may fatally paralyze the heart and the central nervous system. Intravenous injection should be made very slowly.

The therapeutic use of calcium in the absence of demonstrable deficiency of that cation in the blood or extracellular fluids is irrational. In ordinary dietary deficiency the administration of calcium compounds should not take precedence over a remedial diet.

**CALCIUM LEVULINATE-N.F.**—"Calcium Levulinate is a hydrated calcium salt of levulinic acid and contains not less than 97.5 per cent and not more than 100.5 per cent of  $C_{10}H_{14}CaO_6$  calculated on a dry basis, the loss on drying being determined on a separate portion by drying in a vacuum oven at a pressure not exceeding 5 mm. and a temperature of  $60^\circ$  for 5 hours." *N.F.* The structural formula of calcium levulinate may be represented as follows:



**Physical Properties.**—Calcium levulinate occurs as a white, crystalline or amorphous powder, having a faint odor suggesting burnt sugar and a bitter, salty taste. It is freely soluble in water and slightly soluble in alcohol. It is insoluble in ether and in chloroform.

**Actions and Uses.**—Calcium levulinate produces the therapeutic effects of calcium. It may be administered orally or intravenously and is virtually nonirritant for subcutaneous or intramuscular injection.

**Dosage.**—By injection, for adults, 1 Gm. daily or on alternate days; for children, intravenously, 0.2 to 0.5 Gm. Orally, for adults, 4 to 5 Gm. three times a day; for children, 1 to 2 Gm. three times a day.

CHEMO PURO MANUFACTURING CORPORATION

Powder Calcium Levulinate: 30 Gm. and 480 Gm. bottles.

CHICAGO PHARMACAL COMPANY

Solution Calcium Levulinate: 10 cc. ampuls. A solution containing 0.1 Gm. of calcium levulinate in each cubic centimeter.

DIRECT LABORATORIES, INC.

Solution Calcium Levulinate: 10 cc. ampuls. A solution containing 0.1 Gm. of calcium levulinate in each cubic centimeter.

THE S. E. MASSENGILL COMPANY

Solution Calcium Levulinate: 10 cc. ampuls. A solution containing 0.1 Gm. of calcium levulinate in each cubic centimeter.

## CARBACRYLAMINE RESINS

**CARBACRYLAMINE RESINS.**—Carbo-Resin (LILLY).—A mixture of 87.5 per cent of the cation exchangers, carbacrylic resin and potassium carbacrylic resin, and 12.5 per cent of the anion exchanger, polyamine-methylene resin. Two-thirds of the cation exchange mixture is carbacrylic resin (a polyacrylic carboxylic acid resin) and the remainder is the potassium salt of the carbacrylic resin.

**Physical Properties.**—Carbacrylamine resins is a light buff, free-flowing powder without appreciable odor. It is practically insoluble



in dilute acids and alkalis, alcohol, ether and water. All of the powder passes a 100-mesh screen and 75 per cent passes a 200-mesh screen.

**Actions and Uses.**—Carbacrylamine resins is used as an adjunct to increase the fecal excretion of sodium in the treatment of edema caused by abnormal sodium retention by the kidney. It is useful, therefore, in the management of sodium retention accompanying chronic congestive heart failure, cirrhosis of the liver and the nephrotic syndrome.

The cation exchange resin is of the carboxylic acid type that gives up its hydrogen ions in exchange for cations. Its affinity for various cations differs in accordance with their valence and their order in the atomic table. Therefore, in a solution containing equal milliequivalents or concentrations, it would combine with more calcium and potassium than sodium. However, because the concentration of sodium in the intestinal tract is relatively high, the major exchange capacity of the resin is utilized in the removal of that cation. It is estimated that in a man weighing 60 Kg. (132 lbs.), approximately 160 Gm. of endogenous sodium enters the intestine every day along with the usual exogenous intake of 4 to 6 Gm. Some evidence indicates that the cation exchange resin acts chiefly on the exogenous sodium of the diet. Because of the capacity of the cation exchange resin to combine with other essential metallic ions, it has been found necessary to administer one-third of the resin as the potassium salt to prevent serum deficiency of that important cation. Carbacrylamine resins provides two-thirds of the cation exchange resin in the hydrogen form and one-third in the potassium form. The anion exchange resin makes up about one-eighth of the mixture and is added to reduce the tendency to acidosis produced by the cation exchange resin in patients with severe renal impairment caused by the inability of the kidney to manufacture sufficient ammonia. This tendency toward the production of acidosis is not obviated by the use of an ammonium salt in place of the hydrogen form of the carboxylic resin, since the ammonia which would be released is subsequently converted to urea in the liver. The anion exchange resin slightly increases the capacity of the cation exchange resin at the pH of the intestinal contents. Some investigators have observed that the cation exchange resin enhances the diuresis produced by mercurial diuretics. The use of the cation exchange resin is not intended to supplant the use of mercurial diuretics or dietary control of sodium intake. In edematous patients, who already exhibit a minimal urinary excretion of sodium prior to administration of the resin, there is little chance of producing a further reduction through the fecal diversion of dietary sodium.

Carbacrylamine resins must be employed with care to prevent the development of a low sodium syndrome, particularly in patients with an abnormal distribution of that electrolyte in the tissues. Precautions to guard against the development of acidosis are also essential. Periodic determinations of the carbon dioxide combining power and serum chlorides should be made when negative sodium balance has been present for some time after edema



has disappeared. Patients should also be observed regularly for signs of mineral deficiency in other cations, such as calcium. Since hyperpotassemia can occur when urinary excretion is severely limited, the mixture should be used only in patients with adequate kidney function. Use of the potassium salt form as provided by the mixture is contraindicated for patients with anuria. Salt "substitutes" containing potassium should be used sparingly, if at all, because an increase in potassium intake may reduce the efficiency of the cation exchange resin. The mixture should not be employed without adequate laboratory facilities to follow the serum electrolyte pattern. Whenever food consumption is temporarily interrupted or sodium intake reduced, the dosage of the mixture must be adjusted accordingly. Large doses may produce gastro-intestinal discomfort, anorexia, nausea and vomiting; but care is needed to differentiate such symptoms from those caused by sodium depletion. The possibility of fecal impaction in elderly patients should be kept in mind.

**Dosage.**—Carbacrylamine resins is administered orally as a powder which can be dispersed in water. Each gram will remove approximately one milliequivalent (23 mg.) of sodium from the intestinal tract when the patient is on a diet containing at least 1.5 Gm. of sodium (3.7 Gm. of sodium chloride) per day. The number of metallic ions bound to the carboxylic resin decreases as the intake of salt is reduced. On a low sodium diet (0.5 Gm. or less), usually no more than 0.3 milliequivalent (7 mg.) of sodium is removed by each gram of the mixture. The total daily amount must be adjusted to meet the individual requirements of each patient. For patients with abnormal retention of sodium, who require restriction of sodium intake to 1.5 Gm. or less per day plus regular therapy with a mercurial diuretic, 48 Gm. of carbacrylamine resins is usually adequate to maintain an edema-free state when the dietary intake of sodium is increased to 3 Gm. (7.5 Gm. of sodium chloride) per day. The daily dosage may vary with different patients from 40 to as much as 100 Gm.

The usual initial dose is 16 Gm. (two level tablespoonfuls) suspended in 6 ounces of tap water or fruit juice, three times daily, to be taken between meals. The mouth is rinsed free of the particles after each dose. Milk should be avoided because of its high electrolyte content. The suspension should be taken immediately after thorough stirring, but additional water or juice may be taken after each dose. No more than 24 Gm. is advisable for a single dose. When it is necessary to prescribe more than 72 Gm. per day, the number of doses rather than the size of the individual dose should be increased. The maintenance dosage is adjusted on the basis of constant "dry" body weight when either the dietary intake of sodium can be increased or the total dose of the resin mixture reduced until body weight rises. The dosage required to maintain a balance between intake and output of sodium should be reduced by simultaneous moderate restriction of dietary sodium or by administration of a mercurial diuretic. In some persons severely restricted previously, the moderate increase of salt permitted with the administration of the resin mixture has been followed by in-

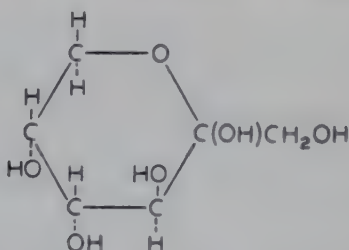
crease in appetite and nutrition. When edema fails to disappear during resin therapy, attention must be given to other factors which may participate in its etiology, such as hypoproteinemia.

#### ELI LILLY & COMPANY

**Powder Carbo-Resin (Flavored):** 8 Gm. packets and 450 Gm. bottles. A flavored mixture containing about 0.583 Gm. of carbacrylic resin, 0.292 Gm. of potassium carbacrylic resin and 0.125 Gm. of polyamine-methylene resin in each gram of powder.

## CARBOHYDRATES

**FRUCTOSE.**—*Levugen* (MEAD JOHNSON).—*Levulose.*—*Fructose* is prepared by the inversion of aqueous solution of sucrose and subsequent separation of fructose from glucose. The structural formula of fructose may be represented as follows:



**Physical Properties.**—A 10 per cent solution is clear and colorless. The pH is 3.0 to 3.5.

**Actions and Uses.**—Fructose (levulose) like dextrose, administered intravenously in solution, is useful for parenteral carbohydrate alimentation when either fluid or calories are required to replace or supplement the oral consumption of water or food. Fructose is metabolized more rapidly and converted more rapidly to liver glycogen than is dextrose. When infused at comparable rates, it results in lower levels of blood sugar and less urinary spillage. Fructose is metabolized or converted to glycogen in the absence of insulin, but the clinical application of this has not been fully determined.

Fructose can be infused at the same rate as, but in twice the concentration of, dextrose, with better retention and less disturbance of fluid balance. Thus, fructose can be employed safely to supply calories more rapidly than either dextrose or invert sugar (half dextrose and half fructose) and to provide more nearly the carbohydrate requirements of patients who need parenteral alimentation. Although fructose is not toxic, excessively rapid intravenous infusion is contraindicated as with other parenteral solutions.

**Dosage.**—Fructose is administered by intravenous infusion as a 10 per cent solution in water. It can be administered at the same rate as a 5 per cent solution of dextrose. The total daily amount required varies with the patient. For adults, the usual initial dose is 1 liter; the average dose, 2 liters; and the maximum dose, 3 liters. For children, the total daily amount is determined on the



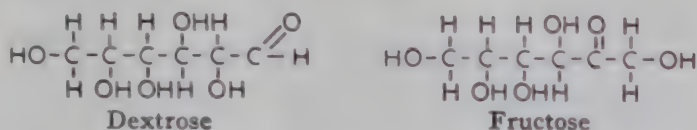
basis of the size and total blood volume of the child. In infants this usually ranges from 0.1 to 1 liter and in children from 0.2 to 2 liters. If administered in quantities in excess of the amounts indicated, any unutilized portion will be excreted in the urine.

Since fructose decomposes in alkaline solution, substances which would raise the pH to values above 7.0 should be added only if the solution is to be administered promptly. Compounds of calcium and barium form insoluble complexes when the pH exceeds 7.0 and are therefore incompatible. Cloudy solutions should not be used.

#### MEAD JOHNSON & COMPANY

**Solution Levugen 10%:** 1 liter bottles. A solution containing 0.1 Gm. of fructose in each cubic centimeter.

**INVERT SUGAR.**—**Travert (BAXTER).**—An equimolecular mixture of dextrose and fructose (levulose) obtained by the inversion of sugar. The structural formulas for dextrose and fructose may be represented as follows:



**Physical Properties.**—Invert sugar solutions are clear and colorless. The solutions have a pH of 3.5 to 6.0.

**Actions and Uses.**—Invert sugar is used in place of dextrose for parenteral carbohydrate alimentation. Its caloric value, gram for gram, is identical with that of dextrose. Evidence, however, indicates that invert sugar is more rapidly utilized than dextrose. The rapidity with which invert sugar is utilized is caused by a more rapid utilization rate of the fructose portion and probably further influence of the fructose upon the glucose portion. Clinical studies indicate that intravenous infusions of 50 Gm. of invert sugar may be given approximately twice as fast as the same amount of dextrose without producing glycosuria. With infusion of larger amounts at this faster rate, the loss of sugar in the urine from invert sugar is only about one-tenth that which occurs from dextrose. This makes it possible to more nearly supply the carbohydrate requirements of patients who need parenteral alimentation.

**Dosage.**—Invert sugar for parenteral carbohydrate alimentation may be administered intravenously, subfascially or subcutaneously. Preparations containing 5 or 10 per cent in either water or isotonic sodium chloride solution are suitable for this purpose and do not subject patients to the discomfort usually accompanying the subcutaneous or subfascial administration of corresponding concentrations of dextrose. One liter of 10 per cent invert sugar supplies approximately 400 calories and can be administered in the same time required for the same quantity of 5 per cent dextrose which supplies approximately 200 calories. Usual precautions taken as with other forms of parenteral alimentation should be observed when administering invert sugar.



## ABBOTT LABORATORIES

**Solution Invert Sugar 5% in Water (or Saline):** Abbo-Liter bottles. A solution in water or isotonic sodium chloride containing 50 mg. of invert sugar in each cubic centimeter.

**Solution Invert Sugar 10% in Water (or Saline):** Abbo-Liter bottles. A solution in water or isotonic sodium chloride containing 0.1 Gm. of invert sugar in each cubic centimeter.

## BAXTER LABORATORIES, INC.

**Solution Travert 5% in Water (or Saline):** 150 cc. and 1 liter bottles. A solution in water or isotonic sodium chloride containing 50 mg. of invert sugar in each cubic centimeter.

**Solution Travert 10% in Water (or Saline):** 150 cc., 500 cc. and 1 liter bottles. A solution in water or isotonic sodium chloride containing 0.1 Gm. of invert sugar in each cubic centimeter.

U. S. trademark 534,117.

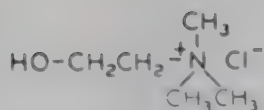
## LIPOTROPIC AGENTS

Five substances possessing lipotropic properties are known to occur in nature, namely choline, betaine, methionine, inositol and  $\beta$ -propiethetin. The latter has been found in seaweed but its presence in materials commonly used for food has not been established. Choline is the best known and apparently most active lipotrope. It also has been used clinically more widely than the others, although comparative studies of lipotropic efficacy are lacking. The naturally occurring "lipotropic" substances also perform other functions in the body which are not associated with their lipotropic activity. Some of them may be used first for other requirements (for example, methionine for growth) before the labile methyl groups become available for lipotropic action. Folic acid and vitamin B<sub>12</sub> (cyanocobalamin) also have some lipotropic effect.

Because the lipotropic effect of these substances was noted first in the liver, they have been employed extensively on this basis in the treatment of liver disease associated with fatty infiltration. In more recent years, they also have been employed in the treatment of atherosclerosis, arteriosclerosis, heart disease and various disorders of lipid metabolism.

While there is definite evidence that these lipotropic substances prevent fatty infiltration in the liver of animals receiving a choline-free diet and that they cause the disappearance of fat from the livers of animals given a hypolipotropic diet, the evidence for their clinical usefulness for such purposes is at present still equivocal.

**CHOLINE CHLORIDE.** — (2-Hydroxyethyl)trimethylammonium chloride.—The structural formula of choline chloride may be represented as follows:



**Physical Properties.**—Choline chloride forms white, deliquescent crystals with an amine-like odor. It is very soluble in water, freely soluble in alcohol and practically insoluble in benzene, chloroform and ether. The pH of a 10 per cent solution is about 4.65.

**Actions and Uses.**—Choline chloride is considered useful as an adjunct in the treatment of fatty infiltration and early cirrhosis of the liver for those patients who cannot take an adequate diet.

**Dosage.**—1.5 to 3 Gm. is administered daily by the oral route, but precise dosage for this and other choline salts is not established.

#### ABBOTT LABORATORIES

**Solution Choline Chloride:** 473 cc. and 3.78 liter bottles. An oral solution containing 0.135 Gm. of choline chloride in each cubic centimeter. Preserved with 0.1 per cent benzoic acid and 0.04 per cent methylparaben.

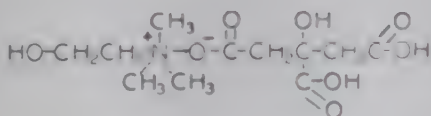
#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Choline Chloride:** Bulk; for manufacturing use.

#### TABLEROCK LABORATORIES

**Elixir Choline Chloride:** 473 cc. and 3.78 liter bottles. An elixir containing 0.2 Gm. of choline chloride in each cubic centimeter. Preserved with 15 per cent propylene glycol and 0.05 per cent butylparaben.

**CHOLINE DIHYDROGEN CITRATE.**—Chothyn Dihydrogen Citrate (FLINT, EATON).—(2-Hydroxyethyl)trimethylammonium citrate.—The structural formula of choline dihydrogen citrate may be represented as follows:



**Physical Properties.**—Choline dihydrogen citrate is a white hygroscopic, crystalline, granular substance, with an acid taste. It melts between 105 and 107.5°. It is freely soluble in water, very slightly soluble in alcohol and practically insoluble in benzene, chloroform and ether. The pH of a 25 per cent solution is about 4.25.

**Actions and Uses.**—Choline dihydrogen citrate shares the actions and uses of other choline salts. See the monograph on choline chloride.

**Dosage.**—2 to 3 Gm. of choline dihydrogen citrate (8 cc. to 12 cc. of the 25 per cent syrup) in divided doses. Choline is always administered orally.

## ABBOTT LABORATORIES

Tablets Choline Dihydrogen Citrate: 0.65 Gm.

## CHEMO PURO MANUFACTURING CORPORATION

Powder Choline Dihydrogen Citrate: 113.4 Gm. bottles.

## FLINT, EATON &amp; COMPANY

Capsules Chothyn Dihydrogen Citrate: 0.5 Gm.

Syrup Chothyn Dihydrogen Citrate: 475 cc. bottles. A flavored syrup containing 0.25 Gm. of choline dihydrogen citrate in each cubic centimeter.

## PHYSICIANS' DRUG &amp; SUPPLY COMPANY

Tablets Choline Dihydrogen Citrate: 0.65 Gm.

## U. S. VITAMIN CORPORATION

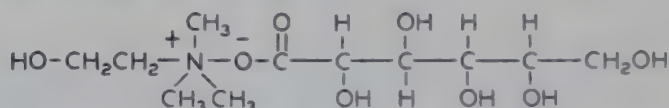
Capsules Choline Dihydrogen Citrate: 0.5 Gm.

## WALKER LABORATORIES, INC.

Capsules Choline Dihydrogen Citrate: 0.25 Gm.

Tablets Choline Dihydrogen Citrate: 0.5 Gm.

**CHOLINE GLUCONATE.**—2-(Hydroxyethyl)-trimethylammonium D-gluconate.—The structural formula of choline gluconate may be represented as follows:



**Physical Properties.**—Choline gluconate is a straw colored, highly viscous mass possessing an aminelike odor and a bitter taste. It is soluble in water, sparingly soluble in alcohol, very slightly soluble in ether and practically insoluble in benzene and chloroform. The pH of a 50 per cent solution is between 5.0 and 6.0.

**Actions and Uses.**—Choline gluconate has the same actions and uses as other salts of choline. See the monograph on choline chloride.

**Dosage.**—Adults: orally, 12 to 15 Gm. daily in three divided doses. 2.46 Gm. of choline gluconate is required to provide the equivalent of 1 Gm. of choline base.

## CHEMO PURO MANUFACTURING CORPORATION

**Solution Choline Gluconate:** Bulk; for manufacturing use. A solution containing 0.58 to 0.62 Gm. of choline gluconate in each cubic centimeter.

## COMMERCIAL SOLVENTS CORPORATION

**Solution Choline Gluconate:** 473 cc. bottles. A flavored solution containing 0.62 Gm. of choline gluconate in each cubic centimeter.



## PARENTERAL FLUIDS

**POTASSIC SALINE (DARROW).**—A mixture of salts available as an aqueous solution containing 0.27 per cent of potassium chloride-U.S.P. (KCl), 0.30 per cent of sodium chloride-U.S.P. (NaCl) and 0.60 per cent of sodium lactate ( $\text{CH}_3\text{CHOHCOONa}$ ) of quality used in sodium lactate injection-U.S.P.

**Physical Properties.**—Potassic saline in solution (Darrow) is a clear, colorless liquid with a pH between 6.5 and 6.7.

**Actions and Uses.**—Potassic saline solution is used parenterally in the treatment of dehydration and acidosis associated with potassium deficiency (particularly that resulting from severe diarrhea). The solution should be employed only when the kidneys are functioning and after initial treatment of shock to ensure adequate circulation. Because of its potassium content and the necessity for caution in administration, potassic saline solution should not be promiscuously employed for restoration of fluids and electrolytes ordinarily replenished with other types of parenteral solutions. Cardiac changes from potassium overdosage may be the only signs of toxicity. Blood potassium determinations and electrocardiographic examinations should be made frequently as precautions against these toxic effects. The blood potassium should be maintained below 20 mg. per 100 cc.

**Dosage.**—Potassic saline solution is administered by hypodermoclysis when possible; by venoclysis only when necessary. The total daily dose should seldom exceed 80 cc. of the solution (0.216 Gm. of potassium chloride) per kilogram of body weight. The rate of administration should be such as to spread the total daily dose over a period of 8 to 12 hours, and administration time over at least 4 hours. For venoclysis in the treatment of severe infant dehydration and diarrhea, dilution of potassic saline solution with one to two parts of a 5 per cent dextrose solution by simultaneous administration via Y-tube connection is advised. Initial treatment of shock with blood or plasma in severely ill patients, or with other parenteral fluids in milder cases, is essential.

For accidental potassium poisoning, 10 per cent of calcium gluconate sufficient to counteract the inhibitory cardiac effect of potassium should be slowly administered by intravenous injection.

DON BAXTER, INC.

**Solution Potassic Saline (Darrow):** 500 cc. Vacoliter bottles. A solution containing 2.7 mg. of potassium chloride, 3 mg. of sodium chloride and 6 mg. of sodium lactate in each cubic centimeter.

# 19

## Oxytocics

**Ergot Preparations.**—Ergot, the dried sclerotium of *Claviceps purpurea* developed on rye, contains a number of specific alkaloids to which it owes its therapeutic effects. In addition, a great variety of chemical substances have been isolated from the crude drug. These include carbohydrates, lipoids, dyes, amino acids and a number of biogenous amines. Among the members of the last group are histamine, tyramine, and acetylcholine, substances which are pharmacologically active but which play a negligible role in the therapeutic effect of the drug.

The alkaloids thus far isolated consist of several pairs of optical isomers, one member of each pair being pharmacologically potent and the other member almost inert. The members of each pair may be interconverted by chemical procedures, and it has been suggested that the inert alkaloids may be formed to some extent from the active ones in the process of extraction.

The isomeric pairs of alkaloids may be listed as follows:

Potent	Relatively Inactive	Formula
1. Ergotoxine	Ergotinine Ψ Ergotinine	$C_{35}H_{39}O_5N_5$
2. Ergotamine	Ergotaminine	$C_{33}H_{35}O_5N_5$
3. Ergosine	Ergosinine	$C_{30}H_{37}O_5N_5$
4. Ergocristine	Ergocristinine	$C_{35}H_{39}O_5N_5$
5. Ergonovine	Ergometrinine	$C_{19}H_{23}O_2N_3$

Various molecular complexes consisting of a potent and an inert alkaloid have also been isolated. These may show a pharmacologic activity different from the average of the activities of their components. In this group may be mentioned sensibamine (ergotamine plus ergotaminine) and ergoclivine (ergosine plus ergosinine).

Common to all of the above alkaloids is a hydrolysis product, lysergic acid ( $C_{16}H_{16}O_2N_2$ ), which contains an indole group. Isomerism in the lysergic acid part of the molecule is believed to account for differences between members of the same pair. The various pairs of alkaloids differ in the other products of hydrolysis, which are unique in the field of alkaloidal chemistry in that certain of them are amino acids. These groups undoubtedly determine the variations in pharmacologic action shown by the active alkaloids of different pairs, e.g., ergotoxine and ergonovine.

**Pharmacology.**—Ergotoxine, ergotamine, ergosine and, presumably, ergocristine show essentially the same type of pharmacologic action although certain individual variations have been observed.

They cause a moderate and prolonged increase in tone and rhythmic contractions of the uterus by direct stimulation of smooth muscle. The blood pressure is increased in the same way, by arteriolar constriction. The effect of epinephrine on the blood pres-



sure may be lessened or reversed through paralysis of the effector responses of the sympathetic nervous system. With sufficient doses cyanosis of the cockscomb and with toxic doses, gangrene through vascular occlusion are caused by direct injury to the capillary endothelium and by persistent vasospasm. Gangrene may also appear clinically on administration of toxic doses. The inhibition of ephedrine action by ergot alkaloids may be demonstrated on other smooth muscle organs, more readily on those such as the rabbit uterus to which the sympathetic nerve supply is predominantly motor. Poisonous doses in the intact animal produce acute manifestations consisting of excitement, tremor, weakness, pyrexia, vomiting and convulsions, due essentially to central stimulation.

Ergotoxine shows slightly greater activity than ergotamine in inhibiting the action of epinephrine on isolated tissues. Ergosine is probably even more potent than ergotoxine in this regard. Ergotamine is only about two-thirds as toxic to white mice as ergotoxine.

Ergonovine is effective on the uterus in smaller doses and concentrations than are the other alkaloids. This difference is particularly apparent in the puerperal state when the uterus is especially sensitive to ergonovine. The uterine action is the only appreciable effect of moderate doses of ergonovine, unpleasant side actions being rare. It is more effective and more prompt in uterine action, when administered orally, than are ergotoxine or ergotamine. Ergonovine increases both the tone and the rate and amplitude of rhythmic contractions of the uterus, the latter effects being proportionately greater than the tonus changes. The duration of effect is less than but comparable to that of ergotoxine and ergotamine. The circulatory effects which are referable to actions on the central nervous system and peripheral vascular mechanism vary with the animal and with experimental conditions. A slight increase in blood pressure may be encountered clinically. Ergonovine shows a definite sympathomimetic effect and little or no inhibition of epinephrine action. Although it produces the characteristic cockscomb reaction, it shows definitely less tendency to produce gangrene than ergotoxine and ergotamine. It is less toxic than these two alkaloids, but in poisonous doses produces similar effects.

All ergot preparations, especially those containing water, deteriorate with age. It is therefore necessary to standardize them, and the date of assay should be indicated on the container.

**Posterior Pituitary Extracts.**—Posterior pituitary contains three types of activity—vasopressor, antidiuretic and oxytocic. Two factors can be separated, vasopressin, which in human beings has vasopressor, antidiuretic and oxytocic activity, and oxytocin. These substances are polypeptides. The response of the human uterus is quite variable to posterior pituitary substances. The reaction depends on the type of extract, condition of the uterus and other factors as yet not understood. In general, large doses may cause uterine tetany lasting up to 10 minutes. This is followed by clonic contractions which diminish in intensity with time. Small doses produce only clonic contractions. Posterior pituitary extracts are ineffective by mouth; being protein, they are destroyed by gastro-intestinal juices. They are effective, however, when applied



to basal mucous membranes, as by injection subcutaneously or intramuscularly. Intravenous injections are hazardous and should not be undertaken except with extremely dilute solutions and under constant and intelligent observation.

The oxytotic properties of posterior pituitary have led to its use for the prevention and the treatment of postpartum and post-abortal uterine atony. It is most effective in the latter case. It has been used in the induction of labor and in cases of uterine inertia during labor. It should never be used under these circumstances except in properly selected cases by capable personnel.

Systemic effects to posterior pituitary are not uncommon. "Obstetrical shock" may follow within a few seconds after intravenous injections and 30 to 60 minutes after subcutaneous injections. The patient complains of anxiety, dyspnea, occasionally precordial pain or she may be symptomless. Circulatory collapse or shock develops. The skin may assume a dusky purple or bright red color. Edema may develop. The patient may succumb. These reactions are considered to be allergic in nature.

**Uses.**—Oxytocics are used widely in the management of the third stage of labor to facilitate the delivery of the placenta, to decrease blood loss and to minimize the likelihood of puerperal complications. The following drug technics are in wide use:

Ergonovine (0.2 mg.) is administered intravenously as the anterior shoulder of the baby stems under the pubic arch. The baby is delivered slowly to allow the drug to exhibit its action. The separated placenta can be expressed almost immediately following the birth of the baby.

Oxytocin (10 units) is administered intramuscularly following the birth of the baby, followed by ergonovine (0.2 mg.) intramuscularly immediately after the delivery of the placenta.

Then no other oxytotic drug is administered until the placenta has been delivered. Ergonovine (0.2 mg.) is administered intramuscularly or intravenously. Posterior pituitary extract (1 cc.) or oxytocin (10 units) is administered intramuscularly. Ergonovine (0.2 to 0.4 mg.) is administered orally and repeated two or three times a day for the first 3 days.

	ERGONOVINE	ERGOTAMINE	POSTERIOR PITUITARY
Time for Effect:			
Oral	6-15 min.	Ineffective	Ineffective
Intramuscular	3-7 min.	15-45 min.	3-7 min.
Intravenous	15-60 sec.	5-45 min.	15-60 sec.
Duration of Effect	3-8 hr.	2-8 hr.	30-60 min.
Average Dose	0.2 mg.	0.5 mg.	1-10 I.U.
Mode of Action	Direct on muscles and sympathetic nerves	Muscle	Muscle
Type of Contraction	Tonic Clonic	Tonic Clonic	Clonic
Method of Assay	Weight	Weight	Biologic
Side Effects	Rare	More common	More common

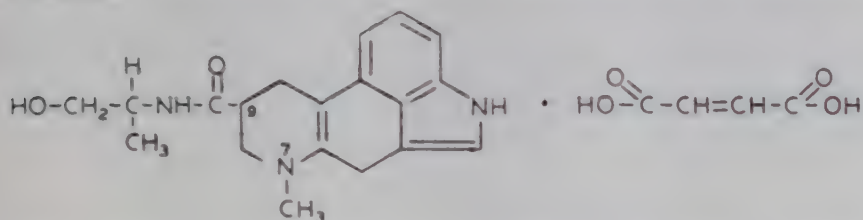
Ergotamine tartrate is of use in migraine headaches. It is not always a prophylactic, and repeated administration will not always

prevent attacks of migraine. Caution is advisable in its use because of the toxicity of overdosage or continued use.

Ergotamine is a very ineffective oxytocic drug even though it may induce uterine contractions and tone similar to ergonovine. It has little place in modern obstetric practice. Orally, ergotamine in contrast with ergonovine is absorbed so irregularly as to be unreliable for oxytocic effect by this route.

Ergotamine is contraindicated in peripheral vascular disease, severe arteriosclerosis and any other condition in which vasoconstriction would be harmful. Side effects are especially common after oral administration. They include nausea, vomiting, abdominal cramps, headache, weakness of the legs and muscle pains of the extremities. Allergic phenomena occur but are rare.

**ERGONOVINE MALEATE-U.S.P.**—Ergotrate Maleate (LILLY).—“Ergonovine Maleate, dried over sulfuric acid for 4 hours, contains not less than 98 per cent of  $C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$ .” *U.S.P.* The structural formula of ergonovine maleate may be represented as follows:



**Physical Properties.**—Ergonovine maleate occurs as a white, or faintly yellow, odorless, microcrystalline powder. It is affected by light. One gram dissolves in about 36 ml. of water, and in about 120 ml. of alcohol. It is insoluble in ether and in chloroform.

**Actions and Uses.**—Ergonovine maleate is a salt of one of the ergot alkaloids possessing oxytocic activity. It is effective on the uterus in smaller amounts than other potent ergot alkaloids. During the puerperium the uterus is especially sensitive to this alkaloid, and it is therefore useful for the prevention and treatment of postpartum hemorrhage. The use of ergonovine maleate in uterine infection is subject to question and, because of its high oxytocic potency, it is also not recommended for routine use prior to delivery of the placenta.

**Dosage.**—Ergonovine maleate may be administered orally, intramuscularly or intravenously. Intravenous injection is preferred in emergencies because of the rapidity of its action. In the placental stage of labor, 0.2 mg. is injected intramuscularly or intravenously after the placenta has been delivered. If it is necessary to repeat the drug because of continued bleeding, a dose of 0.2 mg. should be given intravenously.

In the postpartum period, ergonovine maleate is administered orally in doses of 0.2 to 0.4 mg. The dose is repeated two to three times daily as required to produce firm uterine contraction until the danger of postpartum hemorrhage is past, usually after the first 3 days. In cases of delayed postpartum hemorrhage, a dose



of 0.2 mg. should be given intravenously, followed by oral administration as outlined. For parenteral injection, 0.2 to 0.4 mg. is recommended as a single dose, repeated as necessary until administration by the oral route becomes feasible.

In migraine, doses of 0.2 to 0.4 mg., usually administered orally, may be given every hour until headache is relieved or a total of 2 mg. has been given.

As with other potent ergot alkaloids, prolonged therapy should be avoided and in hypersensitive individuals, care should be taken to prevent the development of ergotism.

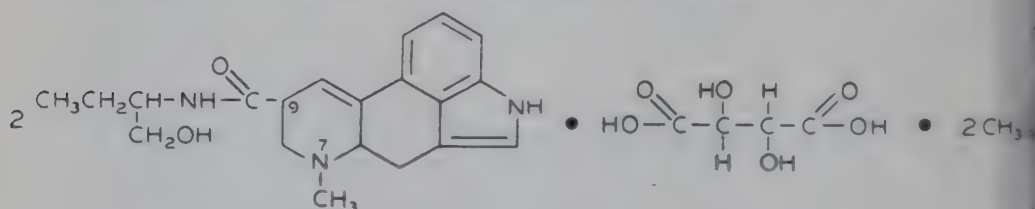
#### ELI LILLY & COMPANY

**Solution Ergotrate Maleate:** 1 cc. ampuls. A solution containing 0.2 mg. of ergonovine maleate in each cubic centimeter.

**Tablets Ergotrate Maleate:** 0.2 mg.

U. S. patents 2,156,242 and 2,220,801. U. S. trademark 323,111.

**METHYLERGONOVINE TARTRATE.**—Methergine Tartrate (Sandoz).—N-[ $\alpha$ -(Hydroxymethyl)propyl]-*d*-lysergamide tartrate containing two molecules of methanol of crystallization.—*d*-Lysergic acid-*d,l*-hydroxybutylamide-2 tartrate containing two molecules of methanol of crystallization.—The structural formula of methylergonovine tartrate may be represented as follows:



**Physical Properties.**—Methylergonovine tartrate is a white to pinkish tan, odorless, bitter, microcrystalline powder. It is very soluble in water, freely soluble in alcohol and very slightly soluble in chloroform and in ether. Methylergonovine tartrate must be protected from light and heat. The pH of a 0.02 per cent solution is 5.0 to 5.8.

**Actions and Uses.**—Methylergonovine tartrate, a partially synthesized derivative of lysergic acid, closely related to ergonovine, is similar in action to the parent compound and other oxytocic alkaloids of ergot. See the general statement on oxytocics and the monograph on ergonovine maleate.

Methylergonovine tartrate induces uterine contractions in the immediate period following placental expulsion and in the puerperium by either parenteral or oral administration (within 30 to 60 seconds after intravenous injection, 2 to 5 minutes after intramuscular injection and 3 to 5 minutes after oral administration). Clinical observations indicate that the intensity and duration of its oxytocic effect is somewhat greater than that of ergonovine maleate but less prolonged than that of ergotamine tartrate.

Methylergonovine tartrate is indicated for administration at the



end of the third stage of labor or cesarean section to prevent or combat postpartum uterine atony and hemorrhage. It appears to have less tendency to produce pressor effects than does ergonovine and, therefore, may be suitable for use in the presence of pre-eclampsia or eclampsia. The drug also may be used to treat subinvolution and to combat secondary puerperal hemorrhage in conjunction with the removal of intrauterine clots. Its use in the presence of uterine infection is open to question.

Methylergonovine tartrate is contraindicated during pregnancy and should not be employed routinely prior to delivery of the placenta; when used under full obstetric supervision, it may be given in the second stage of labor following delivery of the anterior shoulder. Laboratory experience, as well as clinical data on hand at the present, does not show this compound to have any toxic effects that are ordinarily encountered in connection with the use of the ergot alkaloids. Nonetheless the possibility of an unexpected toxic reaction should be borne in mind and physicians should be on the outlook for any untoward effects.

**Dosage.**—Methylergonovine tartrate is administered orally, intramuscularly or intravenously. Injection should be used immediately following delivery of the anterior shoulder or the placenta. A single dose of 0.2 mg. is injected intramuscularly or intravenously at the end of labor. If atony and hemorrhage persist postpartum, further injections of the same dose may be given at intervals of 2 to 4 hours. A dose of 0.2 mg. may be given orally three or four times daily in treating subinvolution or during postpartum convalescence in place of the parenteral route.

SANDOZ PHARMACEUTICALS, DIVISON OF SANDOZ CHEMICAL WORKS, INC.

**Solution Methergine Tartrate:** 1 cc. ampuls. A solution containing 0.2 mg. of methylergonovine tartrate in each cubic centimeter.

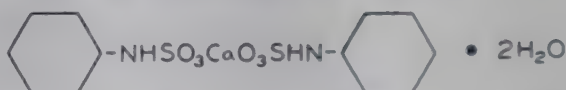
**Tablets Methergine Tartrate, 0.2 mg.**

U. S. patent 2,265,207. U. S. trademark 400,893.

## Pharmaceutic and Therapeutic Aids

This chapter comprises pharmaceutic preparations and substances which do not contain or constitute specific therapeutic agents but which are useful as aids in the formulation of topical medication or in the management and treatment of patients. It includes vehicles, such as ointment bases, suitable for compounding topical preparations of drugs and miscellaneous articles such as substitute sweetening agents and external dusting powders.

**CYCLAMATE CALCIUM.**—*Sucaryl Calcium* (ABBOTT).—Calcium cyclohexylsulfamate dihydrate.—The structural formula for cyclamate calcium may be represented as follows:



**Physical Properties.**—Cyclamate calcium is a white, crystalline, practically odorless powder with a very sweet taste. It is freely soluble in water and practically insoluble in alcohol, benzene, chloroform and ether. The pH of a 10 per cent solution is between 5.5 and 7.5.

**Actions and Uses.**—Cyclamate calcium is a synthetic sweetening agent for use in the diet of diabetics and other patients who must restrict their intake of carbohydrates. It may be used by patients on low sodium diets. Cyclamate calcium is essentially nontoxic, but an excessive intake may produce a laxative effect. This should be controlled by regulation of the amount used in the diet.

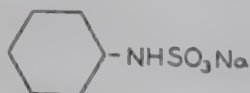
**Dosage.**—Cyclamate calcium is used in the form of a 15 per cent solution for the preparation of foods or to sweeten beverages. 1.25 cc. (one-fourth teaspoonful) of a 15 per cent solution is equivalent in sweetening power to about 2 teaspoonfuls of sugar (sucrose). A bitter taste becomes noticeable when the quantity in foods approaches 0.5 per cent.

### ABBOTT LABORATORIES

**Solution *Sucaryl Calcium*:** 118.3 cc. bottles. A solution containing 0.15 Gm. of cyclamate calcium in each cubic centimeter. Preserved with 0.1 per cent benzoic acid and 0.05 per cent methylparaben.

U. S. patent 2,275,125. U. S. trademark 536,591.

**CYCLAMATE SODIUM.**—Sucaryl Sodium (ABBOTT).—Sodium cyclohexylsulfamate.—The structural formula of sodium cyclamate may be represented as follows:



**Physical Properties.**—Cyclamate sodium is a white, crystalline, practically odorless powder with a very sweet taste. It is freely soluble in water and practically insoluble in alcohol, benzene, chloroform and ether. The pH of a 10 per cent solution of cyclamate sodium is between 5.5 and 7.5.

**Actions and Uses.**—Cyclamate sodium is a synthetic, stable, non-nutritive sweetening agent used as a substitute for sugar by diabetics and others who must restrict the intake of carbohydrate, and as a sweetening agent in oral forms of drugs. It is suitable to replace sugar in the diet when indicated because it is stable in hot solutions, and is free of bitter aftertaste in concentrations below 0.8 per cent. It is about thirty times as sweet as sugar. The sodium content of this preparation is a factor which must be considered in its use in patients with severe kidney damage or other conditions in which dietary sources of sodium are restricted. Cyclamate sodium is essentially nontoxic, but an excessive intake may produce a laxative effect. This should be controlled by regulation of the amount used in the diet. It is somewhat slowly excreted, about 40 per cent unchanged in the urine and 60 per cent unchanged in the feces.

**Dosage.**—0.125 Gm. of cyclamate sodium is approximately equivalent in sweetening effect to 1 teaspoonful of sugar (sucrose). The agent is available in the form of tablets containing 0.125 Gm. of cyclamate sodium with small amounts of sodium bicarbonate and tartaric acid which impart effervescence when the mixture is added to beverages. A solution containing 0.15 Gm. per cubic centimeter is also marketed for its greater convenience in sweetening cold liquids and in preparing special diets.

ABBOTT LABORATORIES, INC.

**Solution Sucaryl Sodium:** 118.4 cc. bottles. A solution containing 0.15 Gm. of cyclamate sodium in each cubic centimeter. Preserved with 0.1 per cent benzoic acid and 0.05 per cent methylparaben.

**Tablets Sucaryl Sodium:** 0.125 Gm.

U. S. patent 2,275,125.

**ABSORBABLE GELATIN FILM.**—Gelfilm (UPJOHN).—A sterile, nonantigenic, absorbable, water-insoluble, gelatin film. Absorbable gelatin film is obtained by drying on plates at constant temperature and humidity a specially prepared gelatin-formaldehyde solution. It is subsequently sterilized by dry heat at 146 to 149° for 12 hours.

**Physical Properties.**—Absorbable gelatin film is a light yellow, transparent, brittle sheet 0.076 to 0.228 mm. thick, with a very



slight, bouillonlike odor and taste. It is practically insoluble in acetic acid and water. It assumes a rubbery consistency after being in water for a few minutes.

**Actions and Uses.**—Absorbable gelatin film is used as an aid in the surgical closure and repair of defects in such membranes as the dura mater and the pleura. It is nonporous and has no hemostatic action. In the dry state, absorbable gelatin film has the appearance and stiffness of cellophane of equivalent thickness, but when moistened, it assumes a rubbery consistency and can be fitted to rounded, irregular surfaces. Its rate of absorption after implantation ranges from 1 to 6 months, depending upon the size of the film employed and the tissue in which it is implanted. Dural implants are less rapidly absorbed than muscle implants. When it is employed as a dural substitute, at least 70 days are required for absorption. This allows sufficient time for healing of the arachnoid layer and formation of new dura, which requires only a few weeks. It also helps to prevent the development of adhesions between the regenerating dura and the arachnoid. Absorbable gelatin film is nonantigenic and does not produce undue inflammatory reaction or other undesirable sequelae.

**Dosage.**—Absorbable gelatin film, which is approximately 0.075 mm. thick, is applied in the form of sheets. Prior to use, the film is soaked in isotonic sodium chloride solution and then cut to the desired shape. For covering dural defects, it is applied to the surface of the brain; the edges are tucked beneath the dura, and the wound is closed in the usual manner. The moist film may be sutured loosely to the dura, but this must be done carefully to avoid tearing the material. For covering pleural defects, a similar technic is followed, except that it is preferable to anchor the film in place by means of small interrupted silk sutures.

Absorbable gelatin film may be stored indefinitely. To avoid contamination, sterile packages should not be opened until the contents are ready to be applied. When necessary, the film can be resterilized at 140° for 4 hours.

#### THE UPJOHN COMPANY

**Gelfilm:** Box of six absorbable gelatin films in individual sterile envelopes; single films are approximately 100 mm. by 125 mm. by 0.16 mm.

U. S. trademark 561,532.

**POLYETHYLENE GLYCOL 300.**—(CARBIDE & CARBON).—White grade.—A polymer having the general formula  $\text{HOCH}_2(\text{CH}_2\text{OCH}_2)_x\text{CH}_2\text{OH}$ , and an average molecular weight of 300. It is a white, viscous liquid, which freezes between  $-15$  and  $8^\circ$ . It is completely miscible with water in all proportions and is useful in the compounding of water-soluble ointment bases and pharmaceuticals for topical applications.

**POLYETHYLENE GLYCOL 1500.**—Carbowax 1500 (CARBIDE & CARBON).—White grade.—A mixture of polyethylene glycols, having

an average molecular weight of about 1550, suitable for the compounding of water-soluble ointment bases. It is a bland, water-soluble, nonvolatile, odorless solid, having the consistency of a low-melting petrolatum. It is insoluble in petroleum ether but completely soluble in water. It melts between 38 and 41°, and the pH of a 5 per cent aqueous solution is about 5.5.

U. S. trademark 380,450.

**POLYETHYLENE GLYCOL 1540.**—**Carbowax 1540** (CARBIDE & CARBON).—A polyethylene glycol having an average molecular weight of about 1540. It is a bland, white, waxy solid which melts between 43 and 46°. It is soluble to form about 70 per cent solutions in water but is insoluble in petroleum ether. The pH of a 5 per cent solution is about 6. It is used in compounding water-soluble ointment vehicles.

U. S. trademark 380,450.

**POLYETHYLENE GLYCOL 4000-U.S.P.**—**Carbowax 4000** (CARBIDE & CARBON).—"Polyethylene Glycol 4000 is a condensation polymer of ethylene oxide and water represented by the formula  $\text{HOCH}_2\text{-(CH}_2\text{OCH}_2\text{)}_n\text{CH}_2\text{OH}$  where  $n$  varies from 70 to 85." U.S.P. It melts between 53 and 56°.

U. S. trademark 380,450.

**STARCH-DERIVATIVE DUSTING POWDER.**—**Bio-Sorb** (ETHICON).—A biologically absorbable powder prepared from cornstarch by etherification with epichlorohydrin. The starch polymer chains are presumably cross-linked by 1,3-diether glycerin groups to the extent of not more than 2 per cent of the original starch weight. The starch derivative is mixed with 2 per cent magnesium oxide, and small residual amounts of sodium sulfate and sodium chloride.

**Physical Properties.**—Starch-derivative dusting powder is an odorless, white powder. The pH of a 10 per cent suspension of starch-derivative dusting powder in water is between 10.4 and 10.8.

No more than 0.1 per cent of starch-derivative dusting powder should be retained on a Tyler 60-mesh screen, no more than 3 per cent on a Tyler 100-mesh screen and no more than 8 per cent on a Tyler 200-mesh screen.

**Actions and Uses.**—Starch derivative dusting powder is a light dusting powder suitable for lubrication of the hands in donning rubber gloves and for other uses to which talcum powder is ordinarily applied in general hospital routines. As a substitute for ordinary powdered talc, it has the advantage of biologic absorbability. It is nonirritating and nontoxic. Therefore its use avoids the hazards of talcum powder.

Starch derivative dusting powder should be sterilized by autoclaving. Slight clumping which occurs after repeated autoclaving may be readily broken up with moderate pressure. Dry wall heat sterilization is not recommended for bacteriologic reasons and should be avoided also because of the possible inflammability of the powder. However, even in contact with red hot cautery, the

powder will flash only to about the same degree as cotton, so that inflammability is not a hazard to its use in surgery.

*Dosage.*—An amount just sufficient to lubricate the skin or article for which a dusting powder is indicated should be applied in the same manner as ordinary talc.

ETHICON SUTURE LABORATORIES

Powder Bio-Sorb: 1.5 Gm. packets and 2.27 Kg. cans.

U. S. trademark 538,336.



## Sclerosing Agents

Solutions of ethyl alcohol, dextrose, invert sugar, iodides, iron salts, mercuric chloride, phenol, quinine and urea hydrochloride, salicylates, sodium chloride, sodium citrate, sodium morrhuate and others have been employed as sclerosing agents, mainly for the obliteration of varicose veins. Some of the compounds employed for this purpose are combined with local anesthetic agents or themselves possess anesthetic properties. Solutions of dextrose or invert sugar and fatty acid preparations such as sodium morrhuate are less irritating; they do not produce necrosis which may occur if more powerful sclerosing substances are accidentally injected outside the vein. Some of the milder agents may be injected in the treatment of selected cases of hemorrhoids, but this form of therapy should not be employed for external prolapsed or thrombosed hemorrhoids. Sclerosing therapy of varicose veins is contraindicated in the presence of incompetency of the collateral deep veins of the lower extremities and before ligation of the greater saphenous vein in the presence of incompetency of the valves of that vein. Other contraindications include active or recent phlebitis, systemic diseases such as active tuberculosis and hyperthyroidism, acute infections (including the common cold), prolonged recumbency, cardiac decompensation and pregnancy. In the occasional case where a patchy dermatitis appears, usually on the legs, and recurs or is exaggerated following succeeding injections of a sclerosing agent, the use of such agents should be discontinued.

**SODIUM MORRHUATE.**—A mixture of the fatty acids of cod liver oil.

**Actions and Uses.**—Sodium morrhuate is a sclerosing agent for the obliteration of varicose veins. It is employed in solution with added local anesthetic. Concentrations of more than 5 per cent are not recommended. Sensitive individuals may develop sensitivity or idiosyncrasy to sodium morrhuate and precautions should be taken to avoid such reactions.

**Dosage.**—0.5 to 1 cc. of a 5 per cent solution is a safe preliminary test dose; its effects should be studied for 24 hours before further injections are made. An average of 1 cc. and a maximum not over 2 cc. may be injected at any one site. Injection of the saphenous vein at the time of ligation may require from 5 to 10 cc. of the 5 per cent solution. The number of injections made in one day varies with the patient and should not comprise a total of more than 5 cc. To guard against the development of sensitivity it is recommended that the interval between the first two injections be no more than 5 days.

## ENDO PRODUCTS, INC.

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 2 and 5 cc. ampuls and 25 cc. bottles. An aqueous solution containing 50 mg. of sodium morrhuate and 20 mg. of benzyl alcohol in each cubic centimeter.

## NATIONAL DRUG COMPANY

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 25 cc. ampul-vials. An aqueous solution containing 50 mg. of sodium morrhuate and 20 mg. of benzyl alcohol in each cubic centimeter.

## ULMER PHARMACAL COMPANY

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 3%:** 5 cc. and 20 cc. vials. An aqueous solution containing 50 mg. of sodium morrhuate, 30 mg. of benzyl alcohol and 5 mg. of phenol in each cubic centimeter.

## THE UPJOHN COMPANY

**Solution Sodium Morrhuate 5% with Benzyl Alcohol 2%:** 2 cc. ampuls and 30 cc. vials. An aqueous solution containing 50 mg. of sodium morrhuate and 20 mg. of benzyl alcohol in each cubic centimeter.

**SODIUM PSYLLIATE.**—*Sylnasol* (SEARLE).—Sodium salt of psyllium oil liquid fatty acids.—Sodium psylliate is a mixture of the sodium salts of the liquid fatty acids prepared by saponification of the vegetable oil of plantago seed (*Plantago ovata*-Forsk). Sodium psylliate is made by dissolving the fatty acids in dilute sodium hydroxide and is not isolated from the solution.

**Physical Properties.**—Solutions (5 per cent with 2 per cent benzyl alcohol) vary in color from light amber to yellow and have a soaplike odor and a slippery feel. They foam readily on shaking. Their pH is between 8.7 and 9.2.

**Actions and Uses.**—Sodium psylliate is used in the form of a 5 per cent solution as a sclerosing agent for the obliteration of varicose veins of the lower extremities and of selected internal hemorrhoids which are not prolapsed or thrombosed. It is not recommended for other types of hemorrhoids.

Its sclerosing action is approximately equivalent to that of other fatty acid salts and it is subject to about the same frequency of allergic reaction to repeated use.

**Dosage.**—A 5 per cent solution of sodium psylliate is injected in amounts dependent upon the size of the varicosity to be obliterated. The dose may vary from a few minims in suitable internal hemorrhoids, to 5 cc. or 6 cc. for large sacculated veins of the lower extremities. The large doses should be given no oftener than twice weekly and single doses in excess of 6 cc. should be avoided. It is advisable to inject a test dose of 0.5 to 1 cc. to detect possible idiosyncrasy before commencing therapy. Treatment should be discontinued when severe reactions occur or are suspected.



G. D. SEARLE & Co.

Sclerosing Solution Sylnasol 5% with Benzyl Alcohol 2%: 5 cc. and 60 cc. vials. An aqueous solution containing 50 mg. of sodium psylliate in each cubic centimeter.

U. S. patents 2,115,491 and 2,115,492; U. S. trademark 340,714.

**SODIUM RICINOLEATE.**—**Soricin (MERRELL).**—The structural formula of sodium ricinoleate may be represented as follows:



**Physical Properties.**—The solution is a clear, odorless, pale yellow liquid. Its pH is not less than 8.2 nor more than 8.5.

**Actions and Uses.**—Sodium ricinoleate, like other fatty acid salts, irritates tissues and, injected in solution, exerts a sclerosing action for the obliteration of varicose veins. Following injection into a varicosity, there is immediate fragmentation of the red blood cells and formation of a jellylike clot, which resists resolution or absorption for a long time. Because of the irritation and destruction of the intima, the thrombus adheres to the wall of the vein. Subsequently there is fibrosis of the vein. Recanalization seldom occurs.

Like other sclerosing solutions, sodium ricinoleate solution is contraindicated for injection of varicose veins in obstruction of the deep (collateral) circulation, phlebitis, infected varicose ulceration, uncontrolled diabetes, arteriosclerosis and hypertension. Since sensitivity or allergic reaction to sodium ricinoleate solutions may occasionally be encountered, it is essential to begin treatment with a test dose as indicated in the following paragraph.

**Dosage.**—All patients should be tested for possible sensitivity to sodium ricinoleate by injection of 0.5 cc. of a 2 per cent solution into a small varicosity 4 or 5 days before actual treatment is started. The drug should not be used in patients who show a reaction to the test dose. Sodium ricinoleate is usually employed as a 2 per cent solution for injection of varicose veins. This is considered the concentration of choice for all but the smallest lesions. A 0.5 per cent solution, agitated to produce a frothy mixture with air to prevent undue hemolysis and subsequent brown pigmentation of the skin, may be used for intradermal injection of small telangiectasia. Superficial venous ruptures (bursts or flares) may be treated with injection of 0.25 to 0.5 per cent concentrations into the most central of the veins involved.

The quantity to be injected depends on the size of the vein and the amount of blood stasis: 2 to 5 cc. of the 2 per cent solution is usually sufficient for injection of the trunk of the great saphenous vein when ligation of that structure is indicated. The average dose of the 2 per cent solution for localized varicosities ranges from 1 to 2 cc., and not more than 10 cc. is recommended for injection of various sites at one administration. Treatments may be repeated at intervals of 1 week. The smallest lesions usually require not more than 0.25 to 0.5 cc. of the drug in the lower concentrations. Care



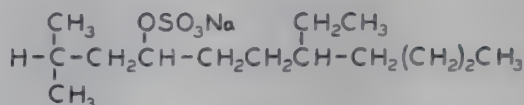
must be taken to avoid extravascular injection of the 2 per cent solution because there is danger of sloughing of tissue.

#### THE WM. S. MERRELL COMPANY

**Solution Soricin Sclerosing 2%:** 20 cc. vials. A solution containing 20 mg. of sodium ricinoleate in each cubic centimeter.

U. S. patent 1,936,456. U. S. trademark 244,397.

**SODIUM TETRADECYL SULFATE.**—Sodium Sotradecol (WALLACE & TIERNAN).—Sodium 7-ethyl-2-methyl-4-hendecanol sulfate.—The structural formula of sodium tetradecyl sulfate may be represented as follows:



**Physical Properties.**—Sodium tetradecyl sulfate is a white, waxy, odorless solid. It is soluble in alcohol, ether and water. A 5 per cent solution is clear and colorless, and has a pH between 6.5 and 9.0.

**Actions and Uses.**—Sodium tetradecyl sulfate is an anionic surface-active agent useful as a wetting agent to increase the surface activity of solutions of certain externally applied antiseptics to which it may be added. It also possesses sclerosing properties useful for the obliteration of varicose veins and internal hemorrhoids which are not prolapsed or thrombosed. Its rather profound sclerosing action is subject to the disadvantage that injections outside of the vein may produce sloughing and that injection into the veins, especially in the higher dosage, may frequently be associated with pain. On the other hand the possibilities of sensitization are remote and the rare idiosyncrasies or anaphylactoid reactions are mild and of short duration. No toxic effects have yet been discovered.

Sodium tetradecyl sulfate is subject to the same contraindications as other sclerosing agents. See the general statement on sclerosing agents.

**Dosage.**—For sclerosis of varicose veins, buffered solutions of sodium tetradecyl sulfate are used; the concentrations employed are 1, 3 or 5 per cent, depending on the size of the veins (amount of hemodilution) to be obliterated. It is recommended that not more than 1 cc. of the 1 per cent concentration be used as a test dose on the first injection to detect idiosyncrasy. The 3 per cent concentration is adequate for most sites. To avoid sloughing that may occur with the use of stronger concentrations in such veins, the 1 per cent concentration should be used for all small superficial varicosities. The average amount to be injected at any site should be 0.5 to 1.0 cc. and at any one sitting, 2 to 3 cc. Not more than 6 cc. of the 5 per cent solution or 10 cc. of the 3 per cent solution should be injected on any one occasion. Repeated injections should be carried out at weekly intervals. Treatment should not be continued if alarming reactions occur.

For sclerosis of uncomplicated internal hemorrhoids the 1 per cent solution of sodium tetradecyl sulfate is recommended; smaller amounts of the 3 per cent solution may be employed, but with a greater risk of sloughing. Higher concentrations should not be used. The initial dose of the 1 per cent solution should be 0.5 cc.; and the dose may be gradually increased to a maximum of 1.5 to 2 cc. at the fifth or sixth injection. When the 3 per cent solution is employed, the initial dose should be 0.2 cc. and the maximum 0.6 cc. Injections should be made at intervals of 5 to 7 days, four to twelve injections being required. Injection too near the anorectal line should be avoided since it may cause pain.

**WALLACE & TIERNAN, INC.**

Solution Sodium Sotradecol with Benzyl Alcohol 2%: 20 cc. vials. A solution containing 10 mg., 30 mg. or 50 mg. of sodium tetradecyl sulfate in each cubic centimeter.

U. S. patent 2,497,742. U. S. trademark 428,131.

## Skeletal Muscle Relaxants and Their Antagonists

Formerly, it was customary to divide the skeletal muscle relaxants into two main groups, those acting on, or in the vicinity of, myoneural juncture and those affecting the basal ganglia and the reflex of excitability of nerve centers. Those that block the myoneural juncture were grouped into the drugs called the curares and the curarelike drugs. This group consisted of the naturally occurring curare alkaloids that act by raising the threshold of the myoneural junction and the synthetic drugs that act by local depolarization. An example of those that act on the reflex excitability would be mephenesin. However, it now appears that the past division into two groups may be less sound than it was originally believed. Both clinical and laboratory evidence indicate that several, possibly most, of the agents that paralyze the neuromuscular end-plate also interfere seriously with the circulation, apparently, in part at least, by block of ganglia.

This entire group of drugs has its chief usefulness in the production of relaxation during surgical anesthesia, in the production of relaxation of muscles for manipulation during orthopedics and similar manipulations, in eye and rectal surgery, for protection against trauma during electric shock, for relaxation of anesthetized muscles and for relaxation of muscles following trauma from operative procedures or from other pathologic states such as back strain, anterior poliomyelitis and various spastic states.

When the skeletal muscle relaxing drugs were first used, it was expected that they would permit a lowering of the operative mortality rate by permitting the surgeon to do effective work under lighter and presumably less hazardous anesthesia than usual. Undoubtedly, the total dose of anesthetic can be diminished for certain operations by the use of these agents; but the increasing evidence indicates that their undoubted advantages have been attained at a price of occasional untoward effects and sometimes of serious difficulty.

It is well known that the skeletal muscle relaxants may cause respiratory failure. The margin of safety between the dose necessary to produce good relaxation of voluntary muscles and that which paralyzes respiration is unfortunately small; but if failure of respiration is detected promptly and treated energetically by artificial respiration and oxygen, recovery is rapid and usually is not accompanied by any untoward after effects. Clearly, facilities



for satisfactory artificial respiration must always be at hand when the muscle relaxants are to be used. Edrophonium chloride may be used as a supplement to these measures, especially after prolonged curarization, but only if some sign of voluntary respiration can be observed. Otherwise, overdosage may result.

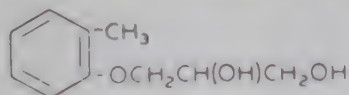
Much more serious than the respiratory problem is the circulatory collapse occasionally seen in patients given these agents, even in dosages not exceeding those usually well tolerated. This circulatory collapse is demonstrated easily in animal experiments after overdosage. This collapse does not always respond to such measures as intravenous injections of blood, blood substitutes or vasoconstrictor drugs. Antidotes, such as neostigmine and physostigmine, are often of little or no assistance and are contraindicated with succinylcholine.

Toxic manifestations suggesting involvement of the central nervous system, effects which again may be demonstrated in animals after overdosage, are seen occasionally in patients after proper doses of these drugs. These serious forms of toxicity may be difficult or impossible to handle satisfactorily.

The operative mortality rate in good hospitals is now low enough so that individual surgeons and anesthetists may not encounter a death for long periods; but certain evidence has led to the contention that operative mortality has been increased significantly when these drugs have been used.

As the muscle relaxants are of great pharmacologic power and are not devoid of danger, they should be used only when an important advantage can be gained for the patient.

**MEPHENESIN.**—Dioloxol (CARNRICK).—Mephson (TUTAG).—Myoxane (ASCHER).—Oranixon (ORGANON).—Sinan (WARREN-TEED).—Tolansin (PHYSICIANS' DRUG).—Tolserol (SQUIBB).—Tolulexin (MILLER).—3-*o*-Toloxyl-1,2-propanediol.—The structural formula of mephenesin may be represented as follows:



**Physical Properties.**—Mephenesin is an odorless, crystalline, white powder which melts between 67 and 72°. It is freely soluble in alcohol, chloroform and ether and sparingly soluble in benzene and water. The pH of the saturated solution is about 6.

**Actions and Uses.**—Mephenesin produces a temporary paralysis superficially resembling that caused by curare but probably differing quantitatively from it in its effect on the basal ganglia, brain stem and thalamus. Suitable doses provide muscular relaxation and relief from certain types of tremor, especially those of Parkinsonism and acute alcoholism. In some cases the tremor may be relieved without the production of muscular weakness. The drug may be tried in any situation in which muscular spasm is present such as cerebral palsy, bursitis, spondylitis and disk syndromes. It has been

tried experimentally in tetanus. Unfortunately the effects of single doses of the drug are often temporary.

The drug has been used to obtain muscular relaxation in surgical anesthesia, but its use for this purpose is decreasing because of the large doses necessary and because in concentrations greater than 1 per cent hematuria may develop. Mephenesin also has a local anesthetic effect.

Mephenesin has a sedative action and it produces a definite, but temporary, improvement in certain psychotic states. The unexpectedly severe sedative action which may result from accumulation of mephenesin with barbiturates is a drawback to its use to secure muscular relaxation during barbiturate anesthesia.

The drug may be used in anxiety tension states as an adjunct to psychotherapy to demonstrate to the patient what is meant by a state of relaxation. Its continued use for such conditions is not advised.

Untoward effects have been infrequent. After intravenous injections, weakness, nystagmus, diplopia and mild muscular incoordination have occurred. Side effects have usually been absent following oral administration, although occasionally lassitude has resulted, and leukopenia has been encountered rarely. The development of tolerance has been suspected.

Mephenesin is of great interest because its action on the central nervous system is unique and the response to it may permit a more accurate localization of diseases affecting the central nervous system.

**Dosage.**—For adults, 1 to 3 Gm. given orally three to five times a day. The dosage should be spread evenly throughout the waking hours. If a favorable response is not seen within 72 hours, the drug should be discontinued.

As a diagnostic aid, 30 to 150 cc. of a 2 per cent solution of mephenesin may be infused intravenously at a rate of 30 to 40 drops per minute.

#### AMERICAN PHARMACEUTICAL COMPANY

Tablets Mephenesin: 0.25 and 0.5 Gm.

#### B. F. ASCHER & COMPANY, INC.

Tablets Myoxane: 0.5 Gm.

#### THE BOWMAN BROS. DRUG COMPANY

Tablets Mephenesin: 0.5 Gm.

#### G. W. CARNRICK COMPANY

Capsules Dioloxol: 0.25 Gm.

Elixir Dioloxol: 473 cc. and 3.78 liter bottles. A solution containing 0.1 Gm. of mephenesin in each cubic centimeter.

Tablets Dioloxol: 0.25 and 0.5 Gm.

U. S. trademark 547,121.

## CHEMO PURO MANUFACTURING CORPORATION

Powder Mephenesin: Bulk; for manufacturing use.

## GOLD LEAF PHARMACAL COMPANY, INC.

Tablets Mephenesin: 0.5 Gm.

## VICTOR M. HERMELIN &amp; COMPANY, DIVISION OF KEITH-VICTOR PHARMACAL COMPANY

Tablets Mephenesin: 0.5 Gm.

## HEXAGON LABORATORIES, INC.

Powder Mephenesin: Bulk; for manufacturing use.

## C. B. KENDALL COMPANY

Tablets Mephenesin: 0.25 Gm. and 0.5 Gm.

## KREMERS-URBAN COMPANY

Tablets Mephenesin: 0.5 Gm.

## E. S. MILLER LABORATORIES, INC.

Elixir Tolulexin: 237 cc. and 3.78 liter bottles. A 5 per cent alcohol, 40 per cent propylene glycol solution containing 0.2 Gm. of mephenesin in each cubic centimeter.

Tablets Tolulexin: 0.25 and 0.5 Gm.

## ORGANON, INC.

Elixir Oranixon: 237 cc., 473 cc. and 3.78 liter bottles. A 20 per cent alcohol solution containing 0.1 Gm. of mephenesin in each cubic centimeter. Preserved with 0.037 per cent methylparaben and 0.025 per cent propylparaben.

Tablets Oranixon: 0.25 and 0.5 Gm.

U. S. trademark 532,165.

## PHYSICIANS' DRUG &amp; SUPPLY COMPANY

Tablets Tolansin: 0.25 and 0.5 Gm.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Mephenesin: 0.25 and 0.5 Gm.

## RAYMER PHARMACAL COMPANY

Tablets Mephenesin: 0.5 Gm.

## REXALL DRUG COMPANY

Tablets Mephenesin: 0.5 Gm.

## E. R. SQUIBB &amp; SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

Capsules Tolserol: 0.25 Gm.

Elixir Tolserol: 473 cc. and 3.8 liter bottles. A solution containing 0.1 Gm. of mephenesin in each cubic centimeter.



**Solution Tolserol:** 50 cc. and 100 cc. ampuls. A solution containing 20 mg. of mephesisin in each cubic centimeter.

**Tablets Tolserol:** 0.25 and 0.5 Gm.

U. S. trademark 527,744.

**S. J. TUTAG & COMPANY**

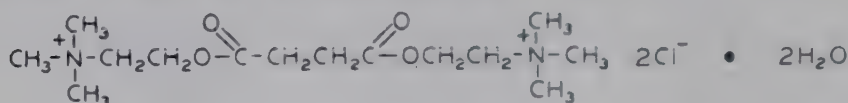
**Elixir Mephson:** 118 cc., 473 cc. and 3.78 liter bottles. An 18 per cent alcohol, 30 per cent propylene glycol solution containing 0.1 Gm. of mephesisin in each cubic centimeter.

**Tablets Mephson:** 0.5 Gm.

**THE WARREN-TEED PRODUCTS COMPANY**

**Tablets Sinan:** 0.5 Gm.

**SUCCINYLCHOLINE CHLORIDE.**—**Anectine Chloride** (BURROUGHS WELLCOME).—**Quelicin Chloride** (ABBOTT).—Choline succinate dichloride dihydrate.—The structural formula of succinylcholine chloride may be represented as follows:



**Physical Properties.**—Succinylcholine chloride is a white, odorless, slightly bitter powder. It is very soluble in water, very slightly soluble in benzene and chloroform and practically insoluble in ether. The amount which dissolves in alcohol to form 100 ml. of solution is 0.42 Gm. Aqueous solutions of succinylcholine chloride are relatively unstable at room temperature. The pH of a 2 per cent solution is 3.0 to 4.5.

**Actions and Uses.**—Succinylcholine chloride is a myoneural blocking agent that produces a skeletal muscle relaxant effect somewhat resembling that of curare and curarelike compounds. It likewise produces muscle relaxation as an adjunct to anesthesia during surgical procedures and in conjunction with electroshock therapy. Succinylcholine chloride is a shorter-acting drug than tubocurarine chloride and, therefore, is particularly suited for endotracheal intubation, endoscopy and other short, manipulative procedures. In contrast with tubocurarine chloride, succinylcholine chloride is not antagonized by anticholinesterases; and the injection of such drugs as physostigmine, neostigmine, procaine or edrophonium prolongs its action. This suggests that the short action of the drug is caused by relatively rapid hydrolysis of the ester linkage by enzyme action, such as that of cholinesterases. Presumably, the drug is hydrolyzed rapidly into nontoxic choline and succinic acid and is not dependent on the liver or kidneys for detoxication or excretion.

Tachyphylaxis or cumulative action is not encountered ordinarily, but like other myoneural blocking agents, succinylcholine chloride in extremely high doses may produce respiratory depres-

sion, persisting after the diaphragmatic response to phrenic nerve stimulation has returned. Facilities for controlled, involuntary respiration and for the administration of oxygen to insure adequate respiratory exchange should be available for combating respiratory paralysis. *Neostigmine or other anticholinesterases and edrophonium are contraindicated as antidotes for succinylcholine chloride.* Succinylcholine chloride should be used with caution in patients with severe liver disease, severe anemia and malnutrition or in those suffering from polyphosphate insecticide poisoning who may have decreased plasma-cholinesterase activity that might intensify and prolong the action of the drug. In such patients, artificial respiration and oxygen therapy may be supplemented by the administration of plasma or whole blood to restore cholinesterase activity.

Because succinylcholine chloride is hydrolyzed rapidly by alkaline solutions, it loses its potency rapidly when mixed with thiopental sodium. For this reason, separate injection is preferable.

Succinylcholine chloride is quite stable when stored under refrigeration. When exposed to room temperature for a long time, its potency gradually decreases; however, biologic assay has shown that solutions may be kept as long as 3 months at room temperature without significant loss of potency.

**Dosage.**—Succinylcholine chloride is administered in solution by the intravenous route, either as a single intermittent injection or as a continuous drip infusion.

For short procedures, the suggested adult dose is 20 mg. for a single injection; the optimum dose ranges from 10 to 30 mg. Within this range each such dose usually produces relaxation in about 1 minute. Maximum muscular relaxation may persist for about 2 minutes, followed by rapid recovery within the next few minutes. Since the maximum safe dosage of the drug has not been determined, and since the response obtained may vary in different patients, careful observation of respiratory exchange is essential to avoid paralytic apnea.

For prolonged procedures, sustained relaxation may be obtained with a continuous intravenous drip infusion at a dosage rate of 0.5 to 10 mg. (average 2.5 mg.) per minute for adults. The solution of the drug to be infused may be prepared by dilution of 500 mg. of succinylcholine chloride in 250 or 500 cc. of sterile isotonic sodium chloride solution or 5 per cent dextrose solution, thus providing a 0.1 per cent (1 mg. per cubic centimeter) or a 0.2 per cent (2 mg. per cubic centimeter) solution, respectively. The degree of relaxation can be altered in approximately 30 seconds by regulating the rate of the drip infusion. Careful supervision of the infusion and the control of respiration are absolutely essential to avoid hypoxia.

#### ABBOTT LABORATORIES

**Solution Quelicin Chloride:** 10 cc. vials. A solution containing 20 mg. of succinylcholine chloride in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.



10 cc. ampuls. A solution containing 50 mg. of succinylcholine chloride in each cubic centimeter.

BURROUGHS WELLCOME & COMPANY, INC.

**Solution Anectine Chloride:** 10 cc. vials. A solution containing 20 mg. of succinylcholine chloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

10 cc. ampuls. A solution containing 50 mg. of succinylcholine chloride in each cubic centimeter.

## CURARE

Curare has frequently been a pharmacologic agent for laboratory investigation but it has only recently come into use as a therapeutic agent. The crude drug is a plant extract prepared by various tribes of South American Indians for use as arrow poisons. The Indians classified types of curare according to the containers in which they were stored. Originally this nomenclature also distinguished chemically different curares. Thus tube curare, pot curare and calabash curare each contained different alkaloids. However, since the changing habits of Indians have rendered the container nomenclature invalid for chemical classification, the chemical distinctions themselves are now used.

Tube curare has been thoroughly investigated. A physiologically active alkaloid called tubocurarine chloride was isolated in crystalline form from this material in 1935. In 1943 it was found in extracts of the plant species *Chondodendron tomentosum*.

The other types of curare, calabash and pot curare, have been less thoroughly examined, but several active crystalline alkaloids have been isolated from calabash curare. The plant species *Strychnos toxifera* in the region of the Orinoco River is the botanical source of this curare. These alkaloids are chemically distinct from those in tube curare. Very little information is available concerning pot curare. Although the active fraction has been identified as a quaternary alkaloid provisionally called protocurarine, it has not been obtained in pure crystalline form. The nature of the other alkaloids associated with this fraction indicate similarity between the alkaloids of pot curare and tube curare.

Curare has been used as a generic term which includes all drugs acting in the vicinity of the myoneural junction. It is sounder, however, to refer to these agents as "the muscle relaxants," since some of the newer agents are not similar to the original curare. It should be emphasized that each drug has its own inherent characteristic pattern of progression of relaxation and also its own inherent pattern of comparative depression of various muscular groups, so that each has a ratio of relaxation dose to total apnea dose. The safety of each of the curares will depend to a degree upon the ratio of the relaxing dose to the apnea dose, the duration of action, and the severity and type of side reaction, such as vascular depression and synaptic or ganglionic blocking action. No one drug of all the curares is superior except in certain characteristics.



Early recognition that the active curare alkaloids are quaternary ammonium bases led to the observation that other quaternary compounds possess varying degrees of curariform activity and to the synthetic preparation of a great number of such compounds. The only compounds which possess curare activity but are not quaternary bases are the Erythrina alkaloids. These alkaloids occur in the seeds of many species of Erythrina; they are tertiary bases but possess true peripheral curare activity.

Curare in therapeutic dosage blocks myoneural transmission to skeletal muscle. Moderate clinical doses also may depress ganglionic transmission in the autonomic nervous system. They also progressively depress the autonomic ganglia, the degree of block varying from drug to drug. In some persons the predominant effect is on the sympathetic nerves, while in others the effect is predominantly on the parasympathetic nerves. These effects have been used clinically to interrupt reflex activity such as vagovagal or vagosympathetic reflexes. The blocking action of curare on the somatic nerves to skeletal muscles is analogous to that of atropine on the parasympathetic nerves to certain smooth muscles. The autonomic action of curare simulates that of nicotine but to a lesser degree and without an initial stimulant phase. Thus, curare is an antispasmodic of skeletal muscle, reducing the tone or contractile power by specific peripheral effect. Some of the synthetic curaremimetic drugs do, however, show the stimulation prior to depression. This becomes evident with the use of such drugs as decamethonium where fibrillatory muscular twitching can be seen prior to the blockade.

Therapeutic doses produce the following sequence of skeletal muscle depression: heaviness of the eyelids; diplopia, except for distant vision; difficulty in swallowing and talking; progressive weakness of extremities and neck, then the trunk and spine, the intercostals, and lastly, the diaphragm. The effect of therapeutic doses depends on such factors as what drug is injected, rate of injection, concentration of drug used, depth and type of anesthesia, over-all body mass, muscular mass and physiologic state of patient. This sequence of depression nearly parallels the order of involvement in myasthenia gravis. Paralysis recedes in reverse order after the full effect is manifest, the extent and duration of action depending on the size of the dose. Recovery may require from 20 to 30 minutes following the ordinary single intravenous dose.

Both physostigmine and neostigmine are pharmacologic antagonists to the muscle-paralyzing effect of curare, but neostigmine is more effective. Neither is adequate to counteract great overdosage and may increase curarization in large doses. Recently, edrophonium chloride has been used to combat overdosage of curariform drugs, with effective results. Atropine should be combined with anticurares to counteract the undesirable side actions, especially the tendency to cause secretion. The excessive use of the anticurares may be detrimental, not only because of their side actions, but also because these drugs, in their bases, potentiate rather than antagonize curare activity. Moreover, prompt and adequate artificial

respiration is the important factor in the treatment of overdosage with curares, and the anticurares are of secondary and limited value.

Curare preparations for therapeutic use are made in partially purified form and in the form of pure or modified tubocurarine. Until more is known of their alkaloidal content, curare preparations from various sources should be bioassayed for potency, although the crystalline chloride salt of tubocurarine may be prescribed on a weight basis. Preparations of *d*-tubocurarine are being prepared with negligible residue and very slight deviation in optical rotation, indicating a great degree of purity. Thus, the drug can now be dispensed by weight alone, the bio-assay being used as a check. The potency of curare is measured by the "head-drop" bio-assay in rabbits and expressed in a unit equivalent in physiologic activity to 0.15 mg. of tubocurarine chloride pentahydrate.

Curare should be employed only by those thoroughly familiar with its dosage, effects and dangers. The anesthetist should have at hand means to establish artificial respiration and to maintain an airway as well as 1 or 2 cc. of neostigmine methylsulfate, 1:2,000, or 1 cc. (10 mg.) of edrophonium chloride for use as an antidote in curare overdosage.

The curares seem to supplement the effect of various anesthetic agents, but tests such as those for analgesic or psychomotor activity and electroencephalogram pattern have not produced evidence to substantiate this clinical impression. Some of the data on the central nervous system's stimulating effect, gained from experiments on animals, is due probably to the anoxia produced by the drug.

Whenever curares are to be used, a test dose should be administered prior to the curarizing dose and allowed to reach its maximal effect. For most of the curares, the time necessary for this is approximately 5 minutes.

Use of curare drugs is hazardous in conditions of shock where peripheral pooling of blood in the venous plexus has resulted from relaxation of the muscles, thus diminishing the cardiac return and subsequently the cardiac output. In addition, many of these drugs block synaptic transmission and therefore cause a peripheral vascular dilatation and potentiate shock. Thus, they should be avoided, especially those that block the synaptic ganglia in states of potential shock.

Repeated dosages of curare drugs should be given with extreme caution because, although persons seem to have emerged from their effects, the actions of curares are greatly prolonged. In fact, at the end of 45 minutes, half of the curare, *d*-tubocurarine, is still available in the body. With repeated dosages the autonomic effects may persist for many hours, thus making the patient vascularly vulnerable as well as diminishing respiratory and other motor functions.

Curare drugs in oil must be used with caution because absorption in most products is not uniform and therefore the response to the drug cannot be predicted. They should be administered only after careful testing and under adequate supervision.



**CHONDODENDRON TOMENTOSUM EXTRACT, PURIFIED.**—**Intocostrin** (SQUIBB).—An aqueous preparation containing therapeutically effective constituents of crude curare. It is prepared by extracting with alcohol a desiccated curare obtained from a heavy syrup of the bark and stems of the *Chondodendron tomentosum*. The curare activity is due almost wholly to the presence of an alkaloid, tubocurarine, which accounts for about half the total solids in purified chondodendron tomentosum extract, exclusive of added sodium chloride and chlorobutanol. The physiologic activity of purified chondodendron tomentosum extract is determined on rabbits: The unit is a potency equivalent to that of 0.15 mg. of a pure or recrystallized tubocurarine chloride pentahydrate containing the theoretical water content of 11.46 per cent.

**Physical Properties.**—Purified chondodendron tomentosum extract is a clear, colorless, aqueous solution, stable to light and heat.

**Actions and Uses.**—Purified chondodendron tomentosum extract is used for the same purposes as its active principle, tubocurarine. See the monograph on tubocurarine chloride.

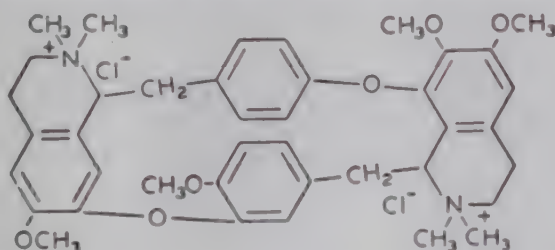
**Dosage.**—See the monograph on tubocurarine chloride.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Solution Intocostrin:** 10 cc. vials. A sodium chloride solution containing the equivalent of 20 units of purified chondodendron tomentosum extract in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

U. S. trademark 382,110.

**DIMETHYL-TUBOCURARINE CHLORIDE.**—**Mecostrin Chloride** (SQUIBB).—O-Methyl-*d*-tubocurarine chloride.—Dimethyl ether of *d*-tubocurarine chloride.—The structural formula of dimethyl-tubocurarine chloride may be represented as follows:



**Physical Properties.**—Dimethyl-tubocurarine chloride is a white, odorless, crystalline powder. It decomposes with evolution of gas when heated to about 236°. It is soluble in water and diluted sodium hydroxide, sparingly soluble in alcohol and diluted hydrochloric acid, very slightly soluble in chloroform and practically insoluble in benzene and ether.

**Actions and Uses.**—Dimethyl-tubocurarine chloride has the same actions and uses as dimethyl-tubocurarine iodide and tubocurarine chloride except that the efficacy of the methylated derivatives in



the treatment of spastic diseases has not yet been determined. (See the monographs on dimethyl-tubocurarine iodide and tubocurarine chloride.)

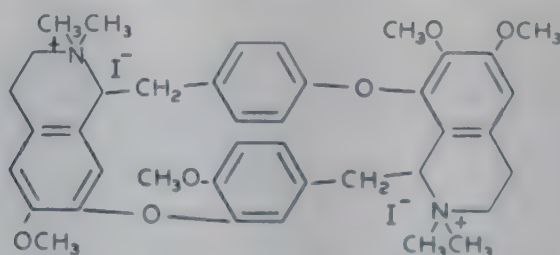
**Dosage.**—Dimethyl-tubocurarine chloride has approximately the same ratio of potency as dimethyl-tubocurarine iodide when compared with tubocurarine chloride, but on the basis of the difference in the molecular weights of the two salts, 0.8 mg. of dimethyl-tubocurarine chloride provides a dose equivalent to 1 mg. of the iodide. Like the iodide, dimethyl-tubocurarine chloride is administered only by slow intravenous injection over a period of 30 to 60 seconds. For muscle relaxation in surgery, the average initial dose for adults is 2 to 3 mg. If needed, 1 to 1.5 mg. can be added in 3 to 5 minutes. After 45 minutes, an additional dose of 1.5 to 2 mg. may be administered. With ether anesthesia the dose of dimethyl-tubocurarine chloride should be about one-third that used with other anesthetic agents. For shock therapy and manipulative therapy the average dose is calculated on the basis of 0.025 mg. per pound of body weight, using 1 mg. less than this amount for the initial dose in adults. The safe upper limit of dosage is 0.037 mg. per pound of body weight. As a diagnostic agent in myasthenia gravis, the dose is one-fortieth to one-tenth of the adult shock therapy dose (i.e., 0.0006 to 0.0025 mg. per pound of body weight), administered intravenously. The test always should be terminated within 2 or 3 minutes by the intravenous injection of 1.5 mg. of neostigmine methylsulfate with 0.6 mg. of atropine sulfate. The same precautions and contraindications should be observed as with other purified derivatives of curare.

E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

**Solution Mecostrin Chloride:** 10 cc. vials. An isotonic salt solution containing 1 mg. of dimethyl-tubocurarine chloride in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol.

U. S. trademark 563,029.

**DIMETHYL-TUBOCURARINE IODIDE.**—Metubine iodide (LILLY).—Dimethyl ether of *d*-tubocurarine iodide.—O-Methyl-*d*-tubocurarine iodide.—The structural formula of dimethyl-tubocurarine iodide may be represented as follows:



**Physical Properties.**—Dimethyl-tubocurarine iodide is a white to pale yellow, odorless, crystalline powder. It decomposes with the evolution of gas when heated to about 257°. It is slightly soluble

in water, diluted hydrochloric acid and diluted sodium hydroxide, very slightly soluble in alcohol and practically insoluble in benzene, chloroform and ether.

**Actions and Uses.**—Dimethyl-tubocurarine iodide shares the curare action of tubocurarine chloride. The methylated derivative of the alkaloid produces respiratory paralysis less frequently. Clinically, the ratio of potency of dimethyl-tubocurarine to *d*-tubocurarine is slightly less than 3:1.

Dimethyl-tubocurarine iodide is useful for the same purposes as tubocurarine chloride, except that its efficacy in the control of spastic conditions has not been completely studied but it would seem to have a greater safety factor because of the relation of its relaxation dose to the apnea dose. See the monograph on tubocurarine chloride.

Like tubocurarine, the methylated derivative is compatible with general anesthetic agents, including the barbiturates employed for this purpose, and is used in conjunction with them to increase skeletal muscle relaxation for certain surgical procedures. See also the general statement on skeletal muscle relaxants.

**Dosage.**—Dimethyl-tubocurarine iodide is administered intravenously in isotonic sodium chloride solution for muscle relaxation in surgery. The average initial dose is approximately 2 mg. and is injected slowly over a period of 30 to 60 seconds, but the size of the initial dose will be influenced by the type of general anesthetic employed; with cyclopropane, 2 to 4 mg. may be required; with ether, 1.5 to 3 mg.; with nitrous oxide and thiopental sodium 3 to 8 mg. Satisfactory relaxation cannot be obtained with initial doses below 1 mg. The initial dose may be expected to provide relaxation for periods ranging from 25 to 90 minutes, or an average of approximately 60 minutes. Supplemental injections of 0.5 to 1 mg. may be made as required and indicated by the depth of surgical relaxation. As with all curare preparations, it is important that the user be experienced in the administration of the drug to avoid the dangerous consequences of overdosage. Respiratory paralysis should be treated promptly by artificial respiration with an airway, until the paralysis has receded. Neostigmine methylsulfate solution 1:2,000 in 1 to 2 cc. doses, or 1 cc. (10 mg.) of edrophonium chloride, should be at hand for intravenous administration to combat respiratory depression, but when this is associated with a fall in blood pressure due to excessive curarization, neostigmine methylsulfate may aggravate the condition of shock.

Like other curarelike drugs, dimethyl-tubocurarine iodide is contraindicated in patients with respiratory embarrassment, pulmonary disease or serious circulatory impairment and in patients with myasthenia gravis, except as a diagnostic measure.

#### CHEMO PURO MANUFACTURING CORPORATION

**Powder Dimethyl-Tubocurarine Iodide:** Bulk; for manufacturing use.

#### ELI LILLY & COMPANY

**Solution Metubine Iodide:** 10 cc. ampuls. An isotonic salt solu-

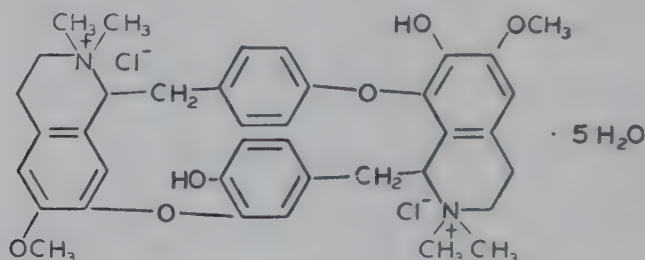


tion containing 0.5 mg. of dimethyl-tubocurarine iodide in each cubic centimeter. Preserved with 0.5 per cent phenol.

10 cc. ampuls and 50 cc. vials. An isotonic salt solution containing 1 mg. of dimethyl-tubocurarine iodide in each cubic centimeter. Preserved with 0.5 per cent phenol.

20 cc. ampuls. An isotonic salt solution containing 2 mg. of dimethyl-tubocurarine iodide in each cubic centimeter. Preserved with 0.5 per cent phenol.

**TUBOCURARINE CHLORIDE-U.S.P.**—*d*-Tubocurarine chloride.—The structural formula of tubocurarine chloride may be represented as follows:



**Physical Properties.**—Tubocurarine chloride occurs as a white or yellowish-white to gray or light tan, odorless, crystalline powder. It melts with slight decomposition at about 270°. One gram of tubocurarine chloride dissolves in about 40 ml. of water and in about 75 ml. of alcohol. It is insoluble in acetone, in chloroform and in ether.

**Actions and Uses.**—Tubocurarine chloride is used to reduce the tone or contractile power of skeletal muscle. It is used with light general anesthesia to obtain greater relaxation of the musculature in abdominal surgery, in special surgery of long duration requiring exceptional management and in orthopedic manipulative procedures. It has also been employed to diminish the violence of muscular contractions during metrazol or electric shock therapy, and temporarily to lessen spasticity due to disease or injury of the central nervous system. Since it aggravates myasthenia gravis symptoms, it has been used in reduced dosage as a diagnostic agent for this condition. See also the general statement on skeletal muscle relaxants.

**Dosage.**—In conjunction with light surgical anesthesia, premedication should be carried out as usual. The following doses are applicable with general anesthetics *except ether, when only one-third of the recommended dose should be employed*. After induction of light surgical anesthesia, 6 to 9 mg. (40-60 units) of tubocurarine chloride may be given in a single intravenous injection for the required muscular relaxation; an additional 3 to 4.5 mg. (20-30 units) may be given in 3 to 5 minutes and repeated later if necessary. The effect usually appears in 3 to 5 minutes. In overdosage, if ventilation is insufficient, but a patent airway exists, adequate pulmonary exchange may be maintained by periodic compression of the bag of the anesthetic apparatus.



In shock treatment as used in psychiatry, the usual dose is 3 mg. (20 units) for each 40 pounds of body weight (for greater safety 3 mg. less than the calculated amount should be used as the initial dose), and the intravenous injection should be given over a period of not less than 90 seconds. In spastic states, where the drug is used to permit training in the voluntary use of muscles, it may be administered intramuscularly. The dose is determined by trial, beginning with 3 mg. (20 units) intramuscularly for each 40 pounds of body weight and gradually increasing the dose until the amount producing the best results is found. As a diagnostic test for myasthenia gravis, 0.3 mg. (2 units) per 40 pounds of body weight is given intravenously; extreme exaggeration of symptoms appears within 2 minutes if myasthenia is present. As soon as a positive reaction is obtained, the curare effect should be antagonized by the intravenous injection of 1 or 2 cc. of neostigmine methylsulfate 1:2,000, combined with 0.6 mg. of atropine sulfate, or 1 cc. (10 mg.) of edrophonium chloride.

*The high potency solution of tubocurarine chloride, 15 mg. (100 units) per cubic centimeter should never be injected without dilution because of the danger of overdosage by too rapid administration.* Tubocurarine chloride-barbiturate combination anesthesia should not be used in patients with pulmonary disorders, renal dysfunction, liver disease, respiratory depression or obstructive states and myasthenia gravis. In fact, since patients react independently to barbiturates and to curare, the use of combinations of these two substances should be avoided.

#### ABBOTT LABORATORIES

**Solution Tubocurarine Chloride:** 10 cc. and 20 cc. vials. A solution containing 3 mg. (20 units) of tubocurarine chloride in each cubic centimeter. Preserved with 0.9 per cent benzyl alcohol and stabilized with 0.1 per cent sodium metabisulfite.

**Solution Tubocurarine Chloride (High Potency):** 1 cc. and 5 cc. ampuls. A solution containing 15 mg. (100 units) of tubocurarine chloride in each cubic centimeter. Stabilized with 0.1 per cent sodium metabisulfite.

#### ENDO PRODUCTS, INC.

**Solution Tubocurarine Chloride:** 10 cc. vials. A solution containing 3 mg. (20 units) of tubocurarine chloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

#### E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

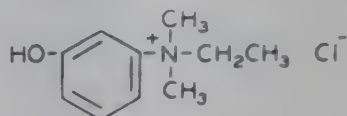
**Solution Tubocurarine Chloride:** 10 cc. and 20 cc. vials. A solution containing 3 mg. (20 units) of tubocurarine chloride in each cubic centimeter. Stabilized with 0.1 per cent sodium bisulfite. Preserved with 0.9 per cent benzyl alcohol.

**Solution Tubocurarine Chloride (High Potency):** 1 cc. ampuls and 10 cc. vials. A solution containing 15 mg. (100 units) of tubocurarine chloride in each cubic centimeter. Stabilized with 0.1 per cent sodium bisulfite.

curarine chloride in each cubic centimeter. Stabilized with 0.1 per cent sodium bisulfite. Preserved with 0.9 per cent benzyl alcohol.

## ANTAGONISTS OF CURARIFORM DRUGS

**EDROPHONIUM CHLORIDE.**—Tensilon Chloride (HOFFMANN-LAROCHE).—Dimethylethyl(3-hydroxyphenyl)ammonium chloride.—The structural formula of edrophonium chloride may be represented as follows:



**Physical Properties.**—Edrophonium chloride is a white, odorless, crystalline powder. It is very soluble in water, freely soluble in alcohol and practically insoluble in ether. The pH of a 1 per cent solution is 4.0 to 5.0.

**Actions and Uses.**—Edrophonium chloride is a competitive antagonist of skeletal muscle relaxants such as tubocurarine, similar-acting curare derivatives and gallamine triethiodide, which produce their effect by interference with the ability of acetylcholine to depolarize the end-plate at the myoneural junction. It displaces such curarelike drugs from their attachment to the muscle cell, permitting resumption of the normal transmission of neuromuscular impulses. Therefore, the drug is useful as an antidote against the peripheral action of curariform agents, either to terminate their therapeutic relaxant effect when it is no longer required or to reverse respiratory muscle paralysis caused by overdosage. Edrophonium chloride does not combat circulatory collapse which is sometimes associated with respiratory depression produced by a central effect of curariform drugs. With extremely large doses, the action of edrophonium becomes curariform and capable of potentiating rather than antagonizing the peripheral paralytic effect of curare. In the presence of apnea, the response to the antidotal action of edrophonium cannot be observed, and there is no clinical guide to effective dosage. For these reasons, the drug should be employed only as a supplement to artificial respiration and oxygen therapy in the treatment of respiratory depression caused by curare overdosage; but, in order to avoid overdosage, edrophonium should be used for this purpose only when some definite sign of voluntary respiration, such as excursion of the diaphragm, can be observed. Under no circumstances should the drug be employed without observing proper precautions in the administration and dosage of curariform agents.

Edrophonium exhibits the parasympathomimetic actions characteristic of neostigmine to some degree, but in the antidotal dosage range it is slightly shorter-acting and produces a lower incidence of side effects. Like the anticholinesterases such as neostigmine, edrophonium prolongs rather than antagonizes the skeletal muscle relaxant action of succinylcholine chloride



and should not be used as an antidote for that drug. Increased salivation and bronchiolar spasm have been reported occasionally in patients with asthma, bradycardia and cardiac dysrhythmia in conjunction with electrocardiographic changes in older patients. The drug, therefore, should be employed with caution in bronchial asthma or cardiac disease. Atropine usually relieves such side effects.

Edrophonium chloride is also useful as a diagnostic agent to differentiate between the presence or absence of myasthenia gravis and for the emergency treatment of myasthenic crises. Its action is too short for maintenance therapy of that disease. Because of its shorter action, edrophonium has the advantage over neostigmine as a diagnostic agent of permitting repeated tests on the same patient several times in an afternoon. The diagnostic use of edrophonium is based upon its ability to produce increased muscle strength without fasciculations when administered to patients with myasthenia gravis. In nonmyasthenic patients the drug produces fasciculations but no increase in strength.

**Dosage.**—As an antidote for curariform drugs, edrophonium chloride is administered by intravenous injection in doses of 10 mg. (1 cc. of a solution containing 10 mg. per cubic centimeter). Smaller doses of 5 mg. each may be adequate for termination of curarization following electroshock therapy. When given to counteract curare overdosage, the effect of each dose on the respiration should be observed carefully before it is repeated, and artificial ventilation always should be employed. The maximal dose for any one patient should be 30 mg. ( $\pm$  10 mg.). Because the action of edrophonium is brief, it should not be given prior to, or as a prophylactic against, the administration of curariform agents. It should be given only at the time its antidotal effect is needed.

As a diagnostic agent in suspected cases of myasthenia gravis, a 10 mg. dose of the drug is injected intravenously. In persons having that disease, increase in muscle strength is observed with maximum improvement occurring within 30 seconds to 5 minutes following injection. In myasthenic crises the drug should be administered by continuous intravenous drip only for the duration of the emergency.

HOFFMANN-LA ROCHE, INC.

**Solution Tensilon Chloride:** 10 cc. vials. A solution containing 10 mg. of edrophonium chloride in each cubic centimeter. Preserved with 0.2 per cent sodium sulfite and 0.5 per cent phenol.

U. S. trademark 570,951.

**NEOSTIGMINE METHYLSULFATE.**—See the monograph in the chapter on autonomic drugs.



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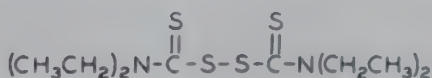
## 23

# Unclassified Therapeutic Agents

A number of drugs of considerable value do not fall under any of the major chapter headings which group preparations of similar or related action or use. Several of these unclassified agents are unique in being the only representatives available for special actions. For convenience, these drugs are brought together in this chapter of miscellaneous agents.

### AGENTS FOR TREATMENT OF ALCOHOLISM

**DISULFIRAM.**—**Antabuse** (AYERST).—Bis(diethylthiocarbamyl) disulfide.—The structural formula of disulfiram may be represented as follows:



**Physical Properties.**—Disulfiram is a white to light gray, odorless and almost tasteless powder. The amounts which dissolve in the following solvents to form 100 ml. of solution are: 3.82 Gm. in alcohol, 7.14 Gm. in ether and 0.02 Gm. in water.

**Actions and Uses.**—Disulfiram, an antioxidant, apparently interferes with the normal metabolic degradation of alcohol in the body, resulting in an increased acetaldehyde concentration in the blood. Perfusion experiments suggest that it acts principally on the enzyme systems of the liver. It does not affect the rate of elimination of alcohol from the body. Regular oral administration of disulfiram, if followed by the ingestion of small amounts of alcohol, causes a highly unpleasant reaction, the severity of which can be correlated with the blood levels of acetaldehyde and ethyl alcohol. It produces no significant effects even after prolonged administration, unless alcohol is introduced into the body. Disulfiram is useful, therefore, for producing a sensitivity to alcoholic beverages as an aid in the treatment of alcoholism. Its use requires the consent and full knowledge of the patient and the application of psychotherapeutic measures designed to rehabilitate the patient. Patients should be advised of the symptoms to be expected if drinking is resumed, and relatives should be instructed concerning the danger of secret administration of the drug. Personality changes have been reported as a consequence of the sudden withdrawal of alcohol, particularly when disulfiram was administered against the

wishes of the patient. A complete history, preferably in the presence of a relative, and a thorough physical examination are essential.

The effectiveness of disulfiram as an aid in overcoming the drinking habit depends upon the demonstration of the unpleasant effects produced following ingestion of even a small amount of alcohol. This is accomplished by administering a trial dose of 15 cc. of 100 proof whisky followed immediately by small amounts of other alcoholic beverages, if such intoxicants might be used by the patient, and demonstrating the reaction produced on others or the patient himself following drug therapy.

Because disulfiram at the dosage now advised is slowly absorbed by the intestinal tract, therapy must be maintained preferably for about 3 weeks before the drug can be counted on to produce a satisfactory reaction to the ingestion of alcohol. Since it is slowly excreted from the intestinal tract, symptoms will follow the ingestion of alcohol taken as long as a week after administration of a single large dose of the drug, indicating that it has a prolonged effect.

The reaction produced by disulfiram and alcohol is characterized by flushing, palpitations, dyspnea, hyperventilation, acceleration of pulse rate, anoxia, fall in blood pressure, nausea, vomiting and occasionally collapse. Drowsiness usually follows with complete recovery after sleep. The severity of the reaction varies with each person and with the amounts of disulfiram and alcohol taken. All types of alcoholic beverages will produce a reaction in patients receiving disulfiram when the blood alcohol concentration is increased to as little as 5 to 10 mg. per 100 cc. Fully developed symptoms are observed at a level of 50 mg. per 100 cc.; unconsciousness occurs at levels of 125 to 150 mg. per 100 cc. Heavy drinkers may tolerate large amounts, but tolerance to alcohol tends to disappear with continued administration of the drug. Tolerance to disulfiram does not develop, nor is it habit forming.

Although disulfiram is of low toxicity when used in the recommended dosage, extreme caution is necessary during its use because severe and alarming reactions to alcohol have been reported in patients on disulfiram. These include cardiovascular complications involving unusual fall in blood pressure, cardiac arrhythmia, electrocardiographic evidence of myocardial ischemia and even myocardial infarction. Such reactions have resulted usually from excessive trial doses of alcohol or surreptitious drinking during initial stages of treatment; therefore, careful and continuous medical supervision is important.

Some patients on disulfiram therapy complain of mild drowsiness, fatigability, impotence, headache or peripheral neuritis, but such symptoms tend to subside with continuation of the drug at a reduced dosage. Because of neurologic changes in animals and toxic psychoses observed in human beings receiving large doses, it is essential to limit the daily dose of the drug. Rare instances of skin eruption, which usually can be controlled by concomitant administration of one of the antihistamine drugs, have been reported.

Although there are no known absolute contraindications, the

alcohol test usually is omitted when disulfiram is to be given to patients over 50 years of age or when used in the presence of diabetes mellitus, goiter, epilepsy, psychosis, cirrhosis of the liver or chronic or acute nephritis. The alcohol test must not be given to patients with myocardial failure, coronary disease or pregnancy. Caution should be exercised when addiction to narcotics is superimposed on alcoholism.

When sedation is required, strict supervision is essential to prevent habituation to barbiturates as a substitute for alcoholism. Disulfiram should not be used in patients recently treated with paraldehyde, and paraldehyde should not be given to patients receiving disulfiram. Disulfiram itself may produce a calming effect conducive to sleep that may lessen the need for sedatives.

**Dosage.**—Disulfiram may be administered orally. The patient should not consume any alcoholic beverage for at least 12 hours before the drug is administered. It is particularly important to refrain from treatment when intoxication is present. The initial dosage should be limited to a maximum of 0.5 Gm. daily for the first 2 or 3 weeks, and subsequent maintenance dosage should not exceed that amount. The usual maintenance dose is about 0.25 Gm., ranging from 0.125 to 0.5 Gm. daily. The dosage should be sufficient for the patient to experience flushing of the face after taking 15 cc. of 100 proof whisky or its equivalent (approximately 7.5 Gm. of 95 per cent alcohol). Uninterrupted administration of the drug should be continued until the patient is socially recovered and a basis for permanent self-control is established. Since therapy depends on the individual patient, it may need to be continued for a period lasting from several months to years. When indicated, a test dose of alcohol is given after the first 2 or 3 weeks of therapy. This should be supervised carefully by the physician, in a hospital if necessary, and a supply of oxygen should be readily available for administration in the event of a severe reaction.

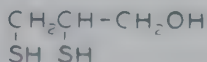
AYERST LABORATORIES, INC.

Tablets Antabuse: 0.5 Gm.

U. S. patent 2,567,814.

## ANTIDOTES FOR HEAVY METAL POISONING

**DIMERCAPROL-U.S.P.—BAL** (HYNSON, WESTCOTT & DUNNING).—“Dimercaprol contains not less than 99 per cent of  $C_3H_8OS_2$ .” U.S.P. The structural formula of dimercaprol may be represented as follows:



**Physical Properties.**—Dimercaprol is a colorless or almost colorless liquid with an offensive, mercaptanlike odor. It is soluble in



water (1 in 13), soluble in alcohol, in methanol and in benzyl benzoate.

**Actions and Uses.**—Dimercaprol in oil is indicated in the treatment of arsenic, gold and mercury poisoning. Results in the treatment of other heavy metal poisoning such as antimony and bismuth have been inconclusive and results in lead poisoning have been disappointing in animal experiments but less certainly so in man.

Dimercaprol, by virtue of being a dithiol, competes with physiologically essential cellular -SH groups for arsenic, mercury and gold, thus preventing combination of the heavy metal with these groups. The stable combination of dimercaprol and heavy metal is rapidly excreted and the body thus freed quickly of the toxic agent.

Dimercaprol is particularly useful in the treatment of hemorrhagic encephalitis due to massive arsenotherapy, arsenical or gold dermatitis and possibly postarsenical jaundice. It is not helpful in homologous serum jaundice or infectious hepatitis. It is useful as an adjunct in the treatment of agranulocytosis due to arsenic, but other measures, principally massive doses of penicillin, must also be employed.

While dimercaprol in oil is indicated in the treatment of mercury poisoning, it must be remembered that mercury causes rapid and extensive tissue damage, particularly to the kidneys, which cannot be corrected by the administration of dimercaprol. The use of dimercaprol in oil in the treatment of mercury poisoning is still in the experimental stage and definite recommendations cannot be made.

The toxicity of dimercaprol is less in patients suffering from arsenic, gold or mercury poisoning, but doses of 300 mg. (5 mg. per kilogram of body weight) may produce nausea, vomiting and headache, a burning sensation of the lips, mouth, throat and eyes, generalized muscular aches with burning and tingling of the extremities and a sense of constriction in the chest. The symptoms usually subside in 30 to 90 minutes.

**Dosage.**—In the treatment of arsenic or gold poisoning, 3 mg. of dimercaprol per kilogram (as a 10 per cent solution in oil) should be administered by intramuscular injection every 4 hours for the first 2 days; four injections should be given on the third day, and two injections daily thereafter for 10 days or until complete recovery. In milder cases, the dose may be reduced to 2.5 mg. per kilogram.

**HYNSON, WESTCOTT & DUNNING, INC.**

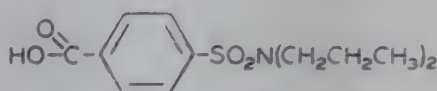
**Solution BAL in Oil:** 4.5 cc. ampuls. A solution in peanut oil containing 10 per cent dimercaprol and 20 per cent benzyl benzoate.

## BLOCKING AGENTS AT THE RENAL TUBULES

A number of drugs, including penicillin, may be actively secreted by the renal tubules, and agents have been sought which would block this action and so maintain the blood levels of the drugs

more easily. Carinamide and more recently probenecid have been used for this purpose. Another recent application of probenecid is in gout, where the excretion of urates is promoted more satisfactorily than with the older salicylates or cinchophens by blocking the urate absorption carrier system of the tubule.

**PROBENECID.**—Benemid (SHARP & DOHME).—*p*-(Dipropylsulfamyl)benzoic acid.—The structural formula of probenecid may be represented as follows:



**Physical Properties.**—Probenecid is a white, odorless, crystalline powder which melts between 198 and 200°. It is soluble in acetone, alcohol, dilute alkalis and dilute sodium bicarbonate and insoluble in dilute acids and water.

**Actions and Uses.**—Probenecid, through a reversible action, interferes with the enzymatic metabolism and inhibits the renal tubular excretion of certain organic compounds such as penicillin, *p*-aminosalicylic acid, and phenolsulfonphthalein. It also acts as a urate eliminant by depressing the renal tubular resorption of urate, thus increasing the urinary excretion and reducing the serum level of uric acid. Probenecid is therefore useful as an adjuvant to intensive therapy with penicillin or *p*-aminosalicylic acid to increase and prolong the plasma concentrations of these anti-infective agents, and as an agent to promote the elimination of uric acid in the interval treatment of gout and the treatment of chronic gouty arthritis. Its suppression of the renal clearance of phenolsulfonphthalein (phenol red) is of significance in the application of that kidney excretion test as a clinical guide to the effectiveness of probenecid. Analytic methods are also available for determination of probenecid metabolites in the body fluids.

Probenecid plasma levels of 2 to 10 mg. per 100 cc. have been correlated with effective plasma levels of penicillin and of *p*-aminosalicylic acid. Probenecid is capable of producing a twofold to tenfold increase in plasma levels of penicillin and a 15 to 50 per cent increase of plasma levels of *p*-aminosalicylic acid. Therefore it can be used to increase the effectiveness of orally administered penicillin and to reduce the dose required for adequate therapy by either the oral or intramuscular route. It may enhance the effectiveness of *p*-aminosalicylic acid in tuberculosis by increasing its plasma level above the usual limits attainable with oral administration without causing gastric distress.

The reabsorption of glucose, arginine, urea or creatinine from the urine is not influenced by probenecid, nor does it affect the excretion of streptomycin, chloramphenicol, aureomycin or terramycin. It raises the plasma concentration of the presumably biologically inactive conjugated sulfonamides, but the insignificant increase it produces in the free sulfonamide level is considered to be therapeutically inconsequential. However, when sulfonamides are administered in conjunction with probenecid, it is suggested



that an occasional sulfonamide plasma determination be made in the same manner that is recommended during any sulfonamide therapy.

Probenecid may precipitate an acute attack of gouty arthritis when used as a urate eliminant in chronic gout. Also, by retarding the urinary reabsorption of urates, it is possible that probenecid may favor the formation of uric acid stones from urates that would tend to crystallize in an acid urine. Colchicine should be administered without discontinuing probenecid to manage acute attacks of gout, and the precipitation of urates can be minimized by maintaining the urine alkaline to litmus. *For the therapy of gout, salicylates should not be administered in conjunction with probenecid because the therapeutic actions of the two drugs are antagonistic.* Probenecid has no analgesic action and is of no value in the treatment of acute gout. Serious anaphylactoid reactions are extremely rare.

Probenecid is rapidly absorbed into the blood stream following oral administration and is promptly eliminated by glomerular filtration. However, its reabsorption by the renal tubules is so great that the renal clearance cannot be estimated because little or none appears in the urine. It is metabolized slowly and its metabolic products are only slowly excreted in the urine. Following a single oral dose, a determinable and functionally useful plasma concentration persists in the dog for longer than 44 hours. A high therapeutic index has been demonstrated in a variety of laboratory animals. Although probenecid is well tolerated in man and is of low toxicity at useful dosages, occasionally patients may experience nausea. This may be overcome by reduction of the daily dosage. Rarely, sensitivity may be manifested by the appearance of a skin rash, but such reactions have been observed much less frequently following therapy with probenecid than following the administration of antibiotics. If a rash appears, therapy with probenecid should be discontinued until the cause of the reaction can be determined.

Probenecid obviously will serve no useful purpose in elevating the plasma concentration of penicillin in the presence of known renal impairment. When there is glomerular involvement, its rapid accumulation in the plasma may cause nausea or other toxic symptoms. Even in the presence of renal damage, probenecid does not exhibit toxic action on the kidney.

**Dosage.**—Probenecid is administered orally. As an adjuvant to penicillin therapy of severe infections such as subacute bacterial endocarditis and staphylococcic osteomyelitis, the total daily dosage in absence of renal disease is 2 Gm. given in four divided doses. The dose should be reduced for older persons in whom renal impairment is more likely to be present. When impairment is sufficient to retard the tubular excretion of penicillin, probenecid is not necessary and may not be tolerated. When used in conjunction with penicillin therapy of children, the daily dosage of probenecid is calculated on the basis of 0.01 to 0.025 Gm. per kilogram of body weight (ranging from 0.25 to 1 Gm.). The dosage of probenecid when used with *p*-aminosalicylic acid is



similar and subject to the same precautions. The phenolsulfonphthalein (phenol red) excretion test employed by the intravenous (15-minute) method can be used as an index of effective plasma concentrations of probenecid. The renal clearance of phenol red is reduced to approximately one-fifth of the normal rate with adequate dosage of probenecid.

As a urate eliminant in chronic gout, a daily single dose of 0.5 Gm. is recommended for 1 week, then increased to 1 Gm. daily in two divided doses. This is usually adequate as a maintenance dose because renal impairment is common in patients with gout. However, for some patients it may be desirable to increase the total daily dosage to 2 Gm., given in four divided doses, to obtain optimal excretion of uric acid. The urine can be maintained alkaline to litmus with doses of 3 to 7.5 Gm. of sodium bicarbonate or 7.5 Gm. of potassium citrate daily, and the patient's acid-base balance should be checked regularly to avoid systemic alkalosis.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Tablets Benemid: 0.5 Gm.**

U. S. patent 2,608,507. U. S. trademarks 547,248 and 567,175.

## BURN DRESSINGS

**ZINCASATE BURN DRESSING.**—Zinax Burn Dressing (HYNSON, WESTCOTT & DUNNING).—Zincasate burn dressing consists of zincasate gel, a partially hydrolyzed casein gel, and zincasate gauze, a zinc acetate impregnated gauze.

**Physical Properties.**—Zincasate gel is a pinkish tan, viscous liquid. The gel has a pH of 6.5 to 7.0. It is readily coagulated by zinc acetate.

**Actions and Uses.**—Zincasate, a combination of partially hydrolyzed casein gel and zinc acetate impregnated gauze to be applied separately, is used as a dressing for the local treatment of burns by the closed pressure bandage technic. The gel, first applied over the injured area, is converted promptly into an insoluble coagulum at the point of contact with the zinc acetate impregnated gauze to form an adherent, protective, semipermeable membrane that permits the evaporation of water while reducing the loss of transudates. The gel will set eventually without the aid of zinc acetate gauze, so that the layer next to the wound is not immediately coagulated. The gauze, through its union with the adherent gel, provides some pressure and a surface to which an elastic bandage can be applied to increase pressure where this is feasible. The combined use of these materials should follow the same general principle and aseptic technic applicable to the use of petrolatum and plain gauze. The use of a coagulable protein and zinc acetate gauze has the slight advantage of convenience of application, avoidance of maceration, less need for redressing and production of a pliable protective film permitting easier movement and transport of the patient.

**Dosage.**—Zincasate gel and gauze dressing are applied after removal of obvious dirt or necrotic tissue, with sterile technic, but

without surgical débridement. The casein gel should be applied to superficial as well as to more deeply injured areas to a thickness of not less than one-eighth inch (0.3 cm.) and should extend beyond the borders of such areas. This then is covered with strips of the zinc acetate impregnated gauze, over which a pressure bandage is applied. Alternatively, the gel may be applied to the gauze, which is then placed over the injured area with the gel side in apposition to the wound. In first degree burns or burns that exhibit only erythema, the dressing usually is removed the following day. In superficial second degree burns, the dressing may be left intact until healing occurs. At that time the dressing will drop away from the wound readily. Earlier removal can be accomplished by soaking the dressing with warm isotonic sodium chloride solution. In deep second and third degree burns, where grafting may be necessary, the surface is frequently ready for grafting within 9 to 12 days. In such cases it is advantageous to hasten removal of necrotic tissue by re-dressing once during this period. In severe burns, the gel film separates readily after the dead skin becomes lysed. It is not necessary to use occlusive bandages on the hands, arms, or face or in other areas where this is not feasible. Gauze is applied longitudinally to the extremities, rather than encircling the limb, to avoid abnormal constriction or pressure at vulnerable points. For small or facial burns, the gel and gauze may be applied as a patch without elastic bandage.

HYNSON, WESTCOTT & DUNNING, INC.

**Zinax Burn Dressing:** 22.18 cc. tubes of zincasate gel packaged with 10 gauze pads and 118.3 cc. cans of zincasate gel packaged with 2 yards of gauze. The gauze is impregnated with approximately 30 per cent zinc acetate by weight.

U. S. patent 2,579,367.

## DERMAL DRYING AGENTS

Sulfur ointments have long been used on the skin, especially in seborrheic dermatitis, where they produce drying and mild irritation. Selenium, which is just below sulfur in the periodic system, presumably acts similarly but apparently is more potent.

**SELENIUM SULFIDE.**—**Selsun Sulfide** (ABBOTT).—Selenium sulfide is a mixture of crystalline selenium monosulfide and solid solutions of selenium and sulfur in an amorphous form, part of which could have the formula  $Se_nS_m$  where  $n$  plus  $m$  equals 8.

**Physical Properties.**—Selenium sulfide is a dull reddish orange to dull brown, amorphous powder. It is odorless, or has a slight sulfide odor, is tasteless and decomposes at about  $100^\circ$ . It is practically insoluble in water and organic solvents. Selenium sulfide reacts with aqua regia to give a clear solution.

**Actions and Uses.**—Selenium sulfide is employed only externally as a liquid suspension for application to the scalp in the treatment of seborrheic dermatitis and the control of seborrhea sicca (dandruff). It may be useful to a lesser extent in the management of



psoriasiform seborrhea, seborrhea oleosa, acne vulgaris and juvenilis and atopic eczema. It is not effective against ringworm of the scalp caused by *Microsporon audouini*.

Selenium sulfide is absorbed through the skin to only a slight degree. Experimental studies indicate that the amount absorbed, when applied as recommended below, is not much greater than the traces which may be present in the average diet. Selenium sulfide is highly toxic if taken orally and patients should be instructed to wash their hands and clean beneath the finger nails to remove all traces of the drug following each external application. The danger of accidental poisoning should be emphasized, and each patient should be warned to keep the drug out of the reach of children. Patients should be advised not to repeat applications unless directed by the physician. External use has not so far revealed any case of intoxication attributed to selenium sulfide. Sensitivity reactions which have been reported in some instances are believed caused by the detergent, alkyl aryl sodium sulfonate, which is present in the commercially available suspension of the drug, although sensitivity to the drug itself may rarely be encountered.

**Dosage.**—Selenium sulfide is applied externally as a suspension containing 2.5 per cent of the agent. For application to the scalp, the hair should be shampooed first with ordinary soap and rinsed. From 5 to 10 cc. of the suspension is then applied by light massage with a small amount of warm water to make a lather. This is allowed to remain in contact with the scalp briefly, then rinsed and the application repeated. The agent should remain in contact with the scalp for a total of at least 5 minutes. The second application should be followed by three or four rinses to remove all traces of the agent. It is recommended usually that such applications be made twice weekly for 2 weeks and then once weekly or less often as indicated.

#### ABBOTT LABORATORIES

**Suspension Selsun Sulfide:** 118.3 cc. bottles. A buffered, stabilized suspension containing a detergent and 25 mg. of selenium sulfide in each cubic centimeter.

## GOLD COMPOUNDS

The clinical use of gold salts in the treatment of arthritis has been in vogue since 1927, and since 1935 has come to be recognized as having some value in selected and carefully supervised cases of progressive rheumatoid arthritis unrelieved by older and safer methods of treatment. Its therapeutic mechanism is not understood. More recently corticotropin, cortisone and hydrocortisone have come into wide use in rheumatoid arthritis, and phenylbutazone has come into perhaps even wider use. These agents have replaced gold compounds to some extent, but gold is still considered a desirable adjunct or alternative by many physicians. Several gold preparations now available offer the advantage of lesser toxicity over the older gold sodium thiosulfate. According to the editorial



review of Philip S. Hench (*Annals of Internal Medicine*, 6:618, 1947), with gold alone over half of the reported patients obtain symptomatic relief, complete in up to a sixth. Up to three-fourths of the improved cases relapse after a time, but may again improve under further treatment. The improvement usually does not begin until the gold injections have been continued for one to three months. This makes it difficult to assign a specific value to the gold treatment, especially as rheumatoid arthritis is potentially reversible without gold. Some skeptical observers consider the results about equal, with or without gold; but more conclude that gold plays a positive role, since the successes have generally been scored on patients in whom other measures have failed. The few control series, including a "blindfold" test, also note improvement rates five to ten times higher with gold than without. However, these chances of usually partial success must be weighed against the risk of very serious toxic reactions in some 5 per cent of the patients. Minor or moderate transient toxicities develop in nearly half the cases.

The intramuscular route, i.e., intragluteal injection, is the preferred method of administration to obtain the systemic effects of gold compounds. Gold is thus eliminated by the kidneys at a much slower rate than it is injected, so that a large cumulation remains in the system for as long as a year after treatment is discontinued. On this account and because of the high incidence of reactions (up to 40 or 50 per cent) attributable to the extremely large doses formerly employed in rheumatoid arthritis (100 to 500 mg. for a total of 1.5 to 2 Gm. in a single course of treatment), the Council was previously hesitant to recognize the use of gold salts for the treatment of that disease.

The advent of more conservative dosage for the treatment of rheumatoid arthritis has greatly reduced the rate of reaction, especially the incidence of serious toxic effects. Experience has shown that therapy should be started with doses of not more than 25 mg. calculated on gold content and continued with gradually increased doses of not more than 50 mg. for women and 75 mg. for men, at weekly intervals, for a total of 500 to 1,000 mg. for a single course of treatment. Total dosage up to 2,000 mg. is sometimes recommended, but the higher the dosage employed, the greater is the chance of reaction—which may be severe or even fatal. Because of this danger, the patient should be examined closely at each visit and a white blood count with differential taken every 2 or 3 weeks. The blood sedimentation rate of fall is a good indication of the effect of therapy.

For several years the Council has recognized the use of gold salts by injection for the systemic treatment of nondisseminated lupus erythematosus.

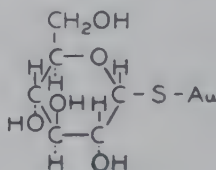
Toxic reactions to gold are of the type caused by other heavy metals, notably arsenicals. The ones to be feared most are exfoliative dermatitis, agranulocytosis, purpura and hepatitis. Any skin reaction demands immediate cessation of further gold therapy and it is doubtful that any patient who has once had a severe reaction should be subjected to further gold therapy. Nitritoid

reactions similar to those seen after arsenicals are sometimes encountered. "Gold bronchitis" and polyneuritis have also been observed. Isolated cases of pigmentation have been reported. Patients should be warned of the deleterious effects of exposure to strong sunlight and should not be given actinotherapy as long as the possibility of photosensitization exists.

Gold therapy should not be employed in nephritis, hepatic disease, anemia, hemorrhagic tendency or other blood dyscrasia, tuberculosis or in acute disseminated lupus erythematosus. Patients with the latter disease are peculiarly likely to show extreme idiosyncrasy for the drugs. Gold therapy should not be used in acute rheumatic fever and is of no value in arthritides other than the active rheumatoid type. It is likewise of little or no value for the chronic stages of rheumatoid arthritis, after extensive deformities have developed.

Dimercaprol (BAL) has been used in the treatment of dermatitis due to aurotherapy. Further discussion of this technic may be found in the monograph on dimercaprol.

**AUROTHIOGLUCOSE.**—*Solganal* (SCHERING).—A gold derivative of thioglucose in which the gold is attached to the glucose molecule through the sulfur atom. The structural formula of aurothioglucose may be represented as follows:



**Physical Properties.**—Aurothioglucose is a yellow to yellow-green powder. It is almost odorless and tasteless. It is soluble in water, but decomposes on standing. It is insoluble in acetone, alcohol, chloroform and ether.

**Actions and Uses.**—Aurothioglucose shares the same therapeutic purposes and toxic manifestations of other organic nonionizing gold compounds; it is used for the treatment of active rheumatoid arthritis and nondisseminated lupus erythematosus. It is harmful in the disseminated form of the latter disease and is subject to the same contraindications and precautions as other injected gold preparations. See the general statement on gold compounds.

**Dosage.**—Aurothioglucose is administered by intramuscular injection in the form of an oil suspension. In active rheumatoid arthritis doses of 25 to 50 mg. weekly are given for a total of 1 Gm., preferably beginning with a dose of 10 mg. If tolerated, treatment may be continued with longer intervals between injections. In nondisseminated lupus erythematosus, biweekly, then weekly, gradually increased doses of 0.1 to 50 mg. are given for a total of not more than 1 to 1.5 Gm.

Treatment of the severe toxic manifestations of gold therapy is discussed in the monograph on dimercaprol.

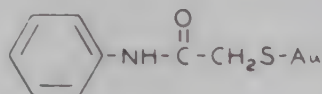


## SCHERING CORPORATION

**Suspension Solganal in Oil:** 10 cc. vials. A suspension in sesame oil containing 10 mg., 50 mg. or 100 mg. of aurothioglucose in each cubic centimeter with 2 per cent aluminum monostearate. Preserved with 0.1 per cent propylparaben.

U. S. trademark 261,372.

**AUROTHIOGLYCANIDE.**—**Lauron** (ENDO).— $\alpha$ -Auomercaptoacetanilid.—The structural formula of aurothioglycanide may be represented as follows:



**Physical Properties.**—Aurothioglycanide is a grayish yellow powder. It is insoluble in acids, bases, benzene, ether, chloroform and water.

**Actions and Uses.**—Aurothioglycanide, a water-insoluble gold compound, is used for the treatment of rheumatoid arthritis on the same basis and subject to the same precautions as water-soluble salts of gold. (See the general statement on gold compounds.) Aurothioglycanide is absorbed more slowly from the tissues than are water-soluble gold compounds and produces fewer untoward reactions, but it should be employed with similar caution to avoid the possibility of toxic reactions. It has not been shown to be more effective than other gold compounds. Careful supervision, repeated laboratory examinations which will reveal signs of gold intoxication and avoidance of exposure to sunlight, ultra-violet rays or x-rays are essential as with the use of other forms of chrysotherapy.

**Dosage.**—Aurothioglycanide is administered into the gluteal muscle by injection of a suspension in oil. The initial dose should not exceed 25 mg. This is increased gradually as tolerated by increments of not more than 25 mg. administered at weekly intervals for 22 weeks. However, a maximum single dose of 150 mg. should not be exceeded. When untoward effects are observed, the schedule of weekly injections should be interrupted until such manifestations have disappeared.

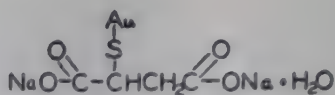
## ENDO PRODUCTS, INC.

**Suspension Lauron in Oil:** 5 and 10 cc. vials. A suspension in sesame oil containing 50 and 150 mg. of aurothioglycanide in each cubic centimeter.

U. S. patent 2,451,841. U. S. trademark 398,432.

**GOLD SODIUM THIOMALATE.**—**Myochrysine** (SHARP & DOHME).—Disodium aurothiomalate.—A gold salt formed by the interaction of sodium thiomalate and a gold halide. It contains about 50 per cent gold. The structural formula of gold sodium thiomalate may be represented as follows:





**Physical Properties.**—Gold sodium thiomalate is a fine, white to yellowish white powder with a metallic taste. It is very soluble in water and practically insoluble in alcohol and in ether. Aqueous solutions of gold sodium thiomalate are colorless to pale yellow. The pH of a 5 per cent solution is between 5.8 and 6.8.

**Actions and Uses.**—Gold sodium thiomalate, like other gold salts, is indicated for the treatment of established cases of active rheumatoid arthritis and for the treatment of nondisseminated lupus erythematosus. Against rheumatoid arthritis it is most effective in relatively early stages before the development of extensive deformities. Gold sodium thiomalate is of no value in the treatment of other arthritides. See also the statement on gold compounds.

**Dosage.**—For active rheumatoid arthritis, an initial intramuscular dose of 10 to 15 mg. is suggested in all patients to test tolerance to the drug. Subsequent doses of 25 to 50 mg. at weekly intervals may be given for a total of 700 to 2,000 mg. as a single course. A total amount not to exceed 500 to 1,000 mg. is considered safer. A minimum of two courses is generally given, with an intervening rest period of 6 to 12 weeks.

For localized lupus erythematosus an initial dose of 5 mg., increased by that amount at weekly intervals to a maximum of 50 mg. for women or 75 mg. for men, usually is recommended.

Toxic reactions are generally minimized by the use of weekly doses not to exceed 25 mg. Transient flushing of the face with giddiness and vertigo may be observed following administration.

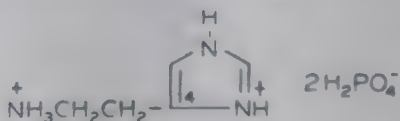
SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Solution Myochrysin:** 1 cc. ampuls. A solution containing 10 mg., 25 mg., 50 mg. or 100 mg. of gold sodium thiomalate, equivalent to 5 mg., 12.5 mg., 25 mg. and 50 mg. of gold, respectively.

U. S. trademark 318,890 assigned to Société des usines Chimiques Rhône-Poulenc, Paris, France.

## HISTAMINE

**HISTAMINE PHOSPHATE-U.S.P.**—The structural formula of histamine phosphate may be represented as follows:



**Physical Properties.**—Histamine phosphate occurs as colorless, odorless, long prismatic crystals. It is stable in air but is affected by light. Its solutions are acid to litmus paper. One gram of histamine phosphate dissolves in about 4 ml. of water.

**Actions and Uses.**—Histamine exists in various organs and tissues

of the body, probably in an inert form. It produces local vasodilatation when released from the cell under appropriate stimuli, such as trauma, shock and possibly allergic reactions. When injected into an animal, histamine stimulates gastric secretion and produces flushing, nausea, bronchospasm, fall in blood pressure, arrhythmia and gastro-intestinal contraction. It acts directly on the receptive substance in smooth muscle.

Histamine, although absorbed orally, produces highly variable effects when administered by this route. Salts of histamine usually are administered subcutaneously, intravenously or intramuscularly.

Histamine phosphate is employed as a test for gastric secretory activity. It also produces a temporary benefit in some patients with Menière's syndrome, including those showing sudden deafness. It has been used in the treatment of multiple sclerosis; although the effects are equivocal, they deserve further study. Some patients apparently experience temporary amelioration of the disease after histamine therapy.

Although histamine has been recommended for treatment of migraine and certain cephalgias, the evidence of value is not convincing. Because of the known hazards of histamine therapy, the drug should not be used indiscriminately in these conditions.

Histamine is a potent drug, and overdosage or administration to susceptible persons may give rise to serious reactions. Vasomotor collapse, shock and even death may occur quickly if the drug is administered too rapidly or in too great a quantity. Thus, when calculating dosages, it should be remembered that the salt contains only about 36 per cent of the active base. Epinephrine hydrochloride is the antidote of choice in histamine overdosage and should be given intramuscularly or, in severe poisoning, intravenously. A solution of epinephrine hydrochloride 1:1,000 always should be readily available at the time histamine is administered.

**Dosage.**—For the treatment of Menière's syndrome and multiple sclerosis, a slow, intravenous injection of histamine phosphate, 1.1 mg. per 100 cc., in isotonic sodium chloride solution may be administered. The initial rate of administration should not exceed 20 to 30 drops per minute and never should exceed 50 to 60 drops per minute. A maximum of 250 cc. of such a solution may be administered in not less than 90 minutes. The therapy may be repeated daily until improvement is noted or until it is determined that the patient will not respond.

*Any reaction is to be treated immediately with the intramuscular or intravenous injection of 1:1,000 epinephrine hydrochloride.*

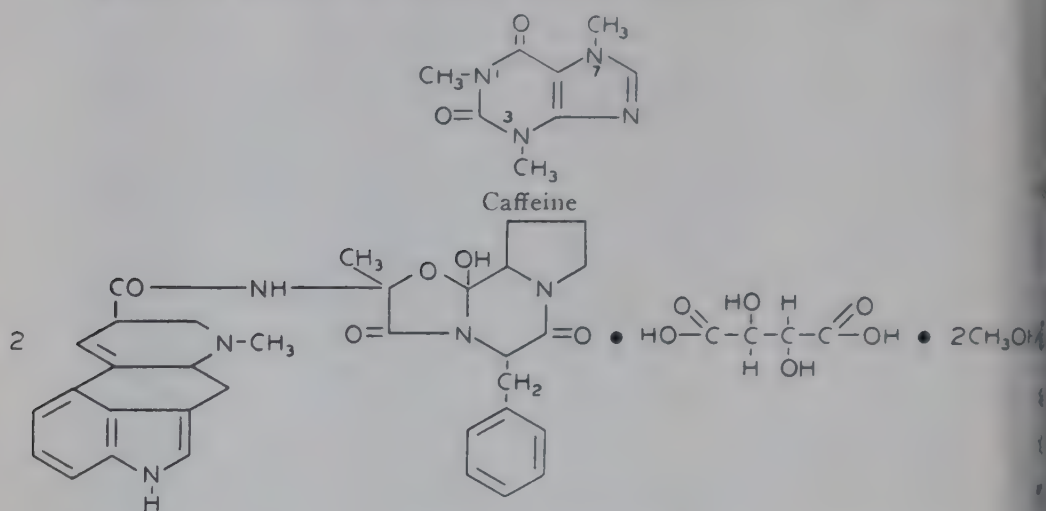
DON BAXTER, INC.

**Solution Histamine Phosphate:** 250 cc. Vacoliter bottles. A solution in isotonic sodium chloride containing 1.1 mg. of histamine phosphate in each 100 cc.

## AGENTS FOR RELIEF OF MIGRAINE

**ERGOTAMINE WITH CAFFEINE.**—*Cafergot* (SANDOZ).—A mixture containing about 1 part of Ergotamine Tartrate-U.S.P. and

100 parts of anhydrous Caffeine-U.S.P. The structural formulas of ergotamine tartrate and caffeine may be represented as follows:



**Actions and Uses.**—Certain investigators have reported that caffeine acts synergistically with ergotamine tartrate and thus lowers the dosage of ergotamine tartrate required for the relief of migraine. Experimental evidence indicates that the addition of caffeine also reduces the toxicity of orally administered ergotamine tartrate.

The effect of the combination is probably brought about by constriction of the cerebral arteries during the vasodilatation phase of the migraine syndrome.

The use of ergotamine tartrate and caffeine is contraindicated in the presence of peripheral vascular diseases, angina pectoris, kidney or liver disease and during pregnancy. The preparation should not be used prophylactically, but merely for the control of migraine attacks.

**Dosage.**—The smallest effective dose of the combination should be determined for each patient. The usual initial dose is 2 mg. of ergotamine tartrate and 200 mg. of caffeine. Subsequent doses of 1 mg. of ergotamine tartrate and 100 mg. of caffeine may be administered at half-hour intervals if the migraine is not relieved. The total dose should not exceed 6 mg. of ergotamine tartrate and 600 mg. of caffeine.

SANDOZ CHEMICAL WORKS, INC.

**Tablets Cafergot:** Each tablet contains 0.1 Gm. of caffeine and 1 mg. of ergotamine tartrate.

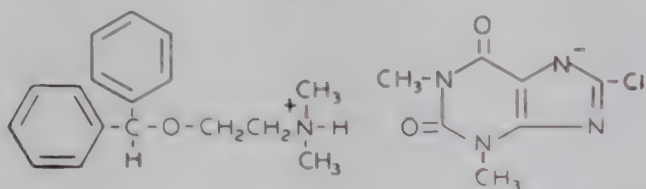
## MOTION SICKNESS REMEDIES

Through the years many preparations have been used for motion sickness. Until recently the most popular were barbiturates, chlorobutanol and various autonomic drugs, especially scopolamine. From



extensive trials during World War II and the years following, it has been demonstrated rather clearly that scopolamine and certain of the antihistamines possess greater potency than the other drugs. Therefore, they now have replaced most of the older preparations in the treatment of motion sickness. Scopolamine and a number of the antihistamines, for instance dimenhydrinate, diphenhydramine and prophenpyridamine, all show about the same degree of action. At times the more diverse side effects of scopolamine make it less satisfactory than the antihistamines, but it is still a substantial alternative or adjuvant.

**DIMENHYDRINATE.** — *Dramamine* (SEARLE). — 2-(Benzohydryloxy)-N,N-dimethylethylamine 8-chlorotheophyllinate.—The structural formula of dimenhydrinate may be represented as follows:



**Physical Properties.**—Dimenhydrinate is a crystalline, white, odorless powder. It is freely soluble in alcohol and chloroform, soluble in benzene, sparingly soluble in ether and slightly soluble in water. It melts between 102 and 107°. The pH of a saturated solution is between 6.8 and 7.3.

**Actions and Uses.**—Dimenhydrinate is a chlorotheophylline salt of the histamine antagonist, diphenhydramine. Its actions are similar to the antihistamine compounds and it shares with them the ability to produce mild sedation of central nervous system origin. Experimentally, the antihistaminic potency of dimenhydrinate is approximately one and one-half times as effective as diphenhydramine. The spasmolytic action of dimenhydrinate is comparatively low and is attributed to its relative insolubility in water. Intravenous injection of the drug in experimental animals produces transient lowering of blood pressure and brief stimulation of respiration. Acute toxicity studies in rats indicate that the LD<sub>50</sub> dose is about 150 mg. per kilogram of body weight, depending on the route of administration. Subacute and chronic toxicity studies in experimental animals have not revealed microscopic evidence of pathologic changes in the heart, liver, kidney or brain. Because of the antihistamine component the danger of prolonged administration should be kept in mind, particularly with respect to possible toxic effects on the hemopoietic system.

Dimenhydrinate is useful in the prevention or treatment of motion sickness. The mechanism of its action in this condition has not been explained completely but is apparently attributable to the diphenhydramine portion of the molecule. It is effective in a high percentage of cases of seasickness, car and train sickness and, to a lesser extent, in airsickness, in which the drug is still a valuable remedy.

The use of dimenhydrinate for the control of nausea and vomiting in motion sickness has led to its use to control these symptoms and that of vertigo in other conditions. Thus, it has been found useful for the management of vertigo in Meniere's syndrome, radiation sickness, hypertension, fenestration procedures, labyrinthitis and vestibular dysfunction associated with streptomycin therapy. It is also useful in the symptomatic control of nausea and vomiting associated with narcotization, electroshock therapy, pregnancy and incidental to therapy with certain other drugs such as aureomycin. Premedication may be useful as a preventive in electroshock therapy.

**Dosage.**—Dimenhydrinate is administered orally or rectally. The usual oral dose for adults is 50 mg., taken one-half hour before departure, for the prevention of motion sickness. This dose may be repeated before meals and on retiring for the duration of the journey. Doses up to 100 mg. may be taken every four hours for motion sickness or to control nausea and vomiting in other conditions, but larger doses are more prone to produce drowsiness. For oral administration to children, two or three times daily: five to eight years of age, 12.5 to 25 mg.; eight to twelve years of age, 25 to 50 mg.; over twelve years, 50 to 100 mg. The same doses may be administered rectally by insertion of the tablet or other suitable form for the treatment of motion sickness or the control of nausea and vomiting in other conditions.

G. D. SEARLE & Co.

Liquid Dramamine: 473 cc. bottles. A solution containing 3.1 mg. of dimenhydrinate in each cubic centimeter.

Tablets Dramamine: 50 mg.

U. S. patent 2,499,058. U. S. trademark 527,862.

## WOUND PROTECTIVES

Drugs with a stimulating action on wound healing have long been desired, and many preparations, such as scarlet red ointment, have been reputed to possess such power. It is probably safe to assume, however, that no substances presently available can promote growth at a more rapid rate than that of normal, optimal healing. Nevertheless, preparations which act as bland protectives may be conducive to wound healing through prevention of crusting and trauma and may reduce offensive odors in some instances.

**WATER-SOLUBLE CHLOROPHYLL DERIVATIVES.**—Chloresium (RYSTAN).—Water-soluble derivatives of chlorophyll consist chiefly of the copper complex of the sodium and/or potassium salts of saponified chlorophyll.

**Physical Properties.**—Water-soluble chlorophyll derivatives present as potassium and/or sodium salts occur as a blue-black glistening powder having an aminelike odor. They are freely soluble in water, slightly soluble in alcohol and chloroform and very slightly soluble in ether. A 1 per cent solution is dark green and has a pH between 9.5 and 10.7.

**Actions and Uses.**—A mixture of the water-soluble derivatives of chlorophyll is employed as a bland, soothing, nonirritating preparation for topical application. A solution or ointment is used for deodorization, normal tissue repair and relief of itching in wounds, ulcers, burns and dermatoses. It does not exert a significant disinfectant action and the mechanism of its deodorant effect on foul-smelling chronic lesions is not clear. Such lesions, which are due primarily to chronic infection, may require surgical intervention and the use of anti-infective agents. Water-soluble chlorophyll derivatives may aid in producing a clean granulating wound base and a condition suitable for the normal repair of tissues. Conclusive evidence is lacking that chlorophyll derivatives stimulate granulation or epithelization beyond the normal rate of healing, but they may overcome retarding factors so as to bring the healing rate up to or toward the normal rate.

**Dosage.**—A solution containing 0.2 per cent water-soluble chlorophyll derivatives is applied topically to the affected areas once, or several times daily, as desired.

An ointment containing 0.5 per cent may be spread over affected areas and covered with fine-mesh gauze or other dressing. Applications are repeated at each change of dressing.

#### RYSTAN COMPANY, INC.

**Ointment Chloresium 0.5%:** 28.35 Gm. and 113.4 Gm. tubes; 454 Gm. jars. An ointment containing 5 mg. of water-soluble chlorophyll derivatives in each gram of water-miscible base.

**Solution Chloresium 0.2%:** 59.14 cc., 236.5 cc. and 946.3 cc. bottles. A solution containing 2 mg. of water-soluble chlorophyll derivatives in each cubic centimeter.

U. S. patents 2,120,667 and 2,434,649. U. S. trademark 408,787.



## Vitamins

Investigations of nutrition since the second decade of the present century have thrown light on many disorders, some of which have long been suspected to be of dietary origin. The investigations demonstrated that dietary factors other than proteins, carbohydrates, fats and minerals are essential for the preservation of bodily well-being and physiologic function. These factors are designated as vitamins.

The absence of any vitamin from a diet which is satisfactory in other respects leads to the development of a typical syndrome called a "deficiency disease." This type of disease may be as striking in its manifestations as are the results of gross underfeeding (caloric deficiency) or deprivation of essential inorganic elements such as iodine, iron, calcium or phosphorus. Scurvy, for example, can be entirely averted or cured by including in the diet foods which contain vitamin C (ascorbic acid). The prophylactic or remedial agent—the antiscorbutic substance—is a chemical entity,  $C_6H_8O_6$ .

A vitamin then is a substance essential for maintenance of normal metabolic functions, not synthesized in the human body in normally adequate amounts. It therefore must be furnished from an exogenous supply. It is sometimes more labile than the food-stuffs proper and hence subject to deterioration, and is distributed among the edible parts of animals and plants. The distinguishing characteristic of the vitamins as a group is the minute quantity in which they are required by the body. More than 20 naturally occurring compounds having vitamin activity have been isolated and identified. All of the well-recognized vitamins, except for carotenes, which are precursors of vitamin A, and vitamin  $B_{12}$ , are produced commercially in synthetic form.

For convenience the designations vitamins A, B, C and D were used. Scurvy, beriberi, rickets, pellagra and xerophthalmia result from the lack of specific vitamins; the protective or curative substances were accordingly spoken of as the antiscorbutic vitamin (C), the antineuritic vitamin ( $B_1$ ), the antirachitic vitamin (D), the pellagra-preventing vitamins (mainly nicotinic acid) and the antixerophthalmic vitamin (A). Most of them now have well established chemical names.

Chemical, physical and microbiologic methods are now used for the determination of vitamins in pharmaceutical products, but biologic assays must be used for vitamin D and for checking other determinations. To facilitate such assays and to make uniform the expression of vitamin content, the World Health Organization of the United Nations has sponsored the preparation and distribution

of standards for vitamins A, B<sub>1</sub>, B<sub>12</sub>, C, D and E. The international unit for each of these vitamins is defined in terms of the biologic activity of a specific quantity of the respective standard. The United States Pharmacopoeial Convention also distributes prototype standards for these six vitamins, and in addition reference standards for several other vitamins. U.S.P. units and international units are identical in value.

It is possible to specify vitamin requirements within narrow limits. A properly selected diet ordinarily affords an adequate supply of vitamins. Furthermore, it is difficult to find evidence of frank deficiency diseases in the adult population of this country. However, restrictions leading to unbalanced diet may cause a shortage of some of the vitamins. The situation can almost always be corrected by prescription of appropriate foods. Occasionally, and particularly with infants, a correction may be more effectively secured by the administration of products rich in the desired vitamin; for example, cod liver oil as a dietary adjunct in the prevention or treatment of rickets, and orange juice in the relief of scurvy.

There are still few indications for specific vitamin therapy. Recognition of special vitamin-bearing products applies to unusual concentrations of the desired potent principle and to exceptionally desirable dosage forms. Multivitamin preparations, particularly capsules, have come into extensive use in recent years. In most of these preparations the proportion of vitamins present bears no relation to established therapeutic dosages, nor to normal requirements for the vitamins. The Council opposes the use of such preparations. It considers only multivitamin preparations in which the vitamin content is in proportion to the daily needs. This subject is discussed in a report published in *J.A.M.A.* 119:948 (July 18) 1942.

A deficiency of any food essential leads to retardation of growth. This is true of each of the essential vitamins but it is equally true of each of the essential amino acids, minerals and energy-yielding compounds.

A person suffering from malnutrition is more susceptible to certain types of infections than the normal individual. But these infections have not been shown to be more closely correlated to specific deficiencies than they are to the organisms to which the body is exposed. Secondary infections are characteristic of conditions resulting from severe vitamin deficiency. The administration of vitamins in excess of bodily needs does not make one more resistant to disease than does the ingestion of quantities just sufficient to meet normal metabolic requirements.

For special provisions and labeling requirements see section on criteria for the evaluation of certain products.

## VITAMIN A

The term "vitamin A" has been applied to several substances and mixtures of these substances which produce a specific demonstrable physiologic effect. A number of chemically related substances pro-

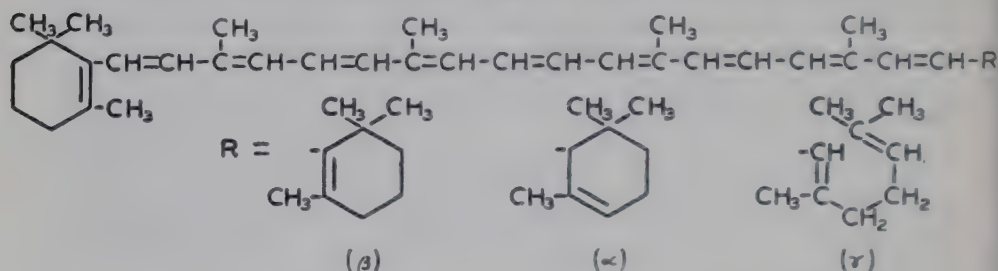


duce this characteristic response in the animal body. These include vitamin A itself; and its precursors, alpha, beta and gamma carotene and cryptoxanthin. The precursors of vitamin A are produced in plants, and in most animals ingestion of these substances results in the formation of varying amounts (depending on the species of animal and the precursor fed) of vitamin A. Vitamin A itself has the empiric formula  $C_{20}H_{29}OH$ . The extent to which the different precursors of vitamin A can be converted to vitamin A by different species of animals varies.

Evidence for the existence of vitamin A and its role in human nutrition is based on the fact that a characteristic eye disease, usually called xerophthalmia, results from a deficiency of this vitamin. Vitamin A is found in fish liver oils and is also produced synthetically.

The unit for vitamin A is defined as the vitamin A activity of 0.3 mcg. of vitamin A alcohol.

**CAROTENE.**—Pro-Vitamin A.—A hydrocarbon having the empiric formula  $C_{40}H_{56}$  which occurs in three isomeric forms referred to, respectively, as alpha, beta and gamma carotene. The structural formulas of these compounds may be represented as follows:



The alpha form is optically active and the others are not. The beta form is the most widely distributed in nature, and the gamma form least widely; but usually a mixture of the different forms occurs. Six-tenths microgram of beta carotene is equivalent in biological activity to 1 unit (0.3 mcg.) of vitamin A. Alpha carotene has approximately one-half the vitamin A activity of beta carotene; gamma carotene has approximately one-third the activity of beta carotene. The term "pro-vitamin A" is regarded by the Council on Pharmacy and Chemistry as a synonym for alpha, beta or gamma carotene and for cryptoxanthin and is used in *New and Nonofficial Remedies* for any combination of two or more of these.

**Actions and Uses.**—Most of the carotene ingested is converted in the intestinal wall into vitamin A. Carotene therefore has actions similar to those of vitamin A. As carotene may be a mixture of the alpha, beta and gamma forms, its efficiency varies according to the ratio of these components. The exact conversion factor of carotene in terms of clinical vitamin A effect is not known. Much depends on the conditions for absorption of pigments. The absorption of carotene and, to a lesser degree, that of vitamin A, is decreased in steatorrhea, chronic diarrhea, chronic biliary obstruction



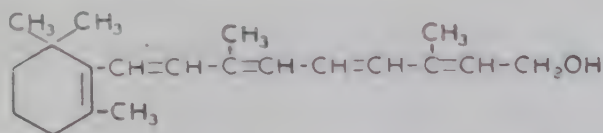
or other impairment of lipid absorption. Liquid petrolatum, being a good solvent for carotene, prevents its absorption, and should not be administered with preparations of carotene. Carotenemia may arise from overdosage with carotene.

**Dosage.**—In comparison with oleovitamin A, approximately twice as many units of carotene are required to produce a given physiologic effect in man. See the monograph on oleovitamin A. Carotene is generally administered dissolved in an oily solution.

WYETH LABORATORIES, INC.

**Capsules Carotene Concentrate in Oil:** Each capsule contains an amount of carotene equivalent to 5,000 U.S.P. units of vitamin A.

**OLEOVITAMIN A-U.S.P.**—Natural Vitamin A in Oil.—“Oleovitamin A is either fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of Vitamin A concentrate, from natural (animal) sources or from synthetic vitamin A or its fatty-acid esters, in fish liver oil or in an edible vegetable oil. Oleovitamin A contains in each Gm. not less than 50,000 and not more than 65,000 U.S.P. units of Vitamin A, and not more than 1,000 U.S.P. units of Vitamin D.” U.S.P. The structural formula of vitamin A may be represented as follows:



**Physical Properties.**—Oleovitamin A is a thin, oily liquid which may have a fishy, but not a rancid, odor and taste.

**Actions and Uses.**—One of the first clinical symptoms of vitamin A deficiency is night blindness, or nyctalopia. For this type of night blindness vitamin A is a specific. Cases of nyctalopia which do not respond to treatment with vitamin A may be due to congenital defects or to other diseases than avitaminosis “A.” The administration of vitamin A to drivers of automobiles does not diminish the chance of night-driving accidents.

Vitamin A is effective in the treatment of certain types of hyperkeratosis of the skin in persons suffering from severe deficiency of vitamin A.

Vitamin A in excess of normal requirements has not been shown to be of value in the prevention of colds, influenza and such infections.

Evidence does not warrant use of vitamin A in the prevention of the formation of renal calculi in man or in the treatment of hyperthyroidism, anemia, degenerative conditions of the nervous system, sunburn or ulcerative conditions of the skin.

**Dosage.**—The minimum daily requirements of vitamin A are 1,500 units for infants, 3,000 units for children and 4,000 for adults. Therapeutic dosages should be at least three times these requirements.

While dosages as large as 100,000 and even 200,000 units daily have been used in certain experimental studies, there is no satisfactory evidence that justifies the use of more than 25,000 units a day. Quantities in excess of those actually needed are stored in the liver and the vitamin is available for future use. Doses in excess of 200,000 units a day are injurious to infants.

AMERICAN PHARMACEUTICAL COMPANY, INC.

**Capsules Oleovitamin A:** Each capsule contains 25,000 U.S.P. units of vitamin A.

BREWER & COMPANY, INC.

**Gel-ets Oleovitamin A:** Each capsule contains 25,000 U.S.P. units of vitamin A.

IVES-CAMERON COMPANY, INC.

**Capsules Oleo Vitamin A:** Each capsule contains 25,000 U.S.P. units of vitamin A derived from fish liver oils.

PREMO PHARMACEUTICAL LABORATORIES, INC.

**Capsules Vitamin A:** Each capsule contains 25,000 U.S.P. units of vitamin A derived from fish liver oils.

WHITE LABORATORIES, INC.

**Capsules Oleovitamin A:** Each capsule contains 25,000 U.S.P. units of vitamin A derived from fish liver oils.

**WATER-SOLUBLE VITAMIN A.**—A concentrate of vitamin A dispersed in water by means of a suitable agent which contains in each gram not less than 50,000 U.S.P. units of vitamin A.

*Actions, Uses and Dosage.*—See the monograph on oleovitamin A.

U. S. VITAMIN CORPORATION

**Aquasol Vitamin A Drops:** 15 cc. and 30 cc. bottles. An aqueous solution containing 50,000 U.S.P. units of natural vitamin A in each cubic centimeter.

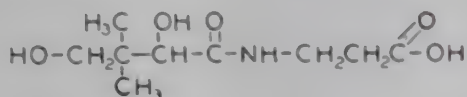
U. S. patent 2,417,299.

## VITAMIN B COMPLEX

The term vitamin B complex is applied to the group of substances which are constituents of what was formerly called vitamin B. Intensive investigations produce an ever-changing picture of the constituents of the complex. Nine members of the vitamin B complex are being manufactured by synthetic processes. Of these, cyanocobalamin, folic acid, nicotinic acid, pyridoxine, riboflavin and thiamine are discussed in the following pages.

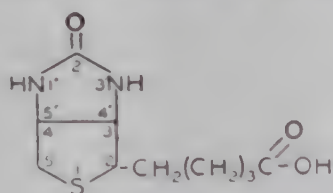
Other members of the group are pantothenic acid and biotin. Pantothenic acid is a factor necessary for the growth of many animals, but its value in human nutrition has not been demonstrated. It is a constituent of an enzyme designated coenzyme A.

which may have important metabolic functions. The structural formula of pantothenic acid may be represented as follows:



Biotin combines with a proteinlike substance in raw egg white called "avidin." In suitable diets containing large proportions of raw egg white, the rat or chick develops characteristic skin lesions and growth is retarded. These symptoms can be prevented by ingestion of biotin. The practical significance of these observations is not established because there is evidence that sufficient quantities of biotin for metabolic requirements may be synthesized in the intestinal tract.

The structural formula of biotin may be represented as follows:



In addition to these compounds there are other factors that have been shown to be essential nutrients for a few species of experimental animals. None of these has been shown to have any importance in human nutrition.

**VITAMIN B COMPLEX.**—A concentrated extract of dried brewer's yeast and an extract of corn processed with *Clostridium acetobutylicum*.

**Actions and Uses.**—Proposed for prophylaxis and treatment of conditions arising from deficiency of the vitamin B complex.

**Dosage.**—See the monographs on the individual components of the vitamin B complex.

MARVIN R. THOMPSON, INC.

**Syrup Vitamin B Complex:** 178 cc., 473 cc. and 3.78 liter bottles. Each cubic centimeter contains 0.3 mg. of thiamine hydrochloride, 0.2 mg. of riboflavin, 0.1 mg. of pyridoxine hydrochloride, 1.4 mg. of niacin and niacinamide and other vitamin B complex factors extracted from 2 Gm. of dried brewer's yeast.

VICO PRODUCTS COMPANY

**Syrup Vitamin B Complex:** 178 cc. bottles. Each cubic centimeter contains 0.3 mg. of thiamine hydrochloride, 0.2 mg. of riboflavin, 0.1 mg. of pyridoxine hydrochloride, 1.4 mg. of niacin and niacinamide, and other vitamin B complex factors extracted from 2 Gm. of dried brewer's yeast.

U. S. patent 2,193,876.



## Cyanocobalamin

**CYANOCOBALAMIN.**—Bevidox (ABBOTT).—Rametin (BIORAMO).—Vitamin B<sub>12</sub>.—Crystalline Vitamin B<sub>12</sub>.—"Vitamin B<sub>12</sub> is a cobalt-containing substance usually produced by the growth of suitable microbial organisms, or obtained from liver. When assayed by the U.S.P. method . . . , it has a purity of not less than 95 per cent, calculated on the anhydrous basis." U.S.P.

Cyanocobalamin is slowly inactivated in solutions of strong acids or alkalis, but in saline solution it withstands autoclaving for 15 minutes at 121°. If kept under sterile conditions, the drug in isotonic saline solution can be stored at room temperature for more than a year without significant loss of therapeutic activity.

**Physical Properties.**—Cyanocobalamin occurs as dark red crystals or as a crystalline powder. One gram dissolves in about 80 ml. of water. It is soluble in alcohol but is insoluble in acetone, in chloroform and in ether.

**Actions and Uses.**—Cyanocobalamin possesses hemopoietic activity apparently identical with that of the anti-anemia factor of liver. However, it has not been established as the complete or essential counterpart of that substance. Studies thus far indicate it to be clinically efficacious in the treatment of pernicious anemia with or without neurologic complications and also in the treatment of tropical and nontropical sprue and nutritional macrocytic anemia resulting from vitamin B<sub>12</sub> deficiency. It is effective only in certain cases of megaloblastic anemia of infancy. The drug is particularly useful in the treatment of patients who are sensitive to liver extract. Cyanocobalamin is fully as effective as liver extract in patients with spinal cord lesions associated with pernicious anemia.

Animal experiments have shown no evidence of toxic effects, either local or systemic, from oral or subcutaneous administration of cyanocobalamin, and no toxic reactions in man have been reported.

**Dosage.**—Cyanocobalamin is extremely potent, and while data are as yet insufficient to warrant exact estimates of the minimum or optimum effective dosage, the minimum is believed to be approximately 1 mcg. per day, or multiples of this amount at corresponding intervals, e.g., 15 mcg. every 2 weeks. The effectiveness of the dosage may be judged by hematologic findings and altered accordingly. One microgram of the drug is estimated to be about equal biologically to one U.S.P. "injectable" unit of liver extract, but further study is necessary to determine accurately the comparative clinical potency of these two agents.

The dosages recommended for parenteral administration are as follows: In uncomplicated pernicious anemia, 15 mcg. once or twice a week until remission occurs, then a maintenance dose of 15 mcg. every other week. In pernicious anemia with neurologic complications, 15 to 30 mcg. once or twice a week until remission occurs, then a maintenance dose of 15 mcg. every other week. In sprue, 15 to 30 mcg. once or twice a week will usually induce remission,

but 15 mcg. once a week thereafter is often necessary to prevent relapse. In nutritional macrocytic anemia in children or adults, a single dose of 15 mcg. usually is sufficient to produce a favorable initial response, but it may sometimes be necessary to repeat this dose at 2-week intervals to prevent relapse.

Recent studies dealing with oral administration indicate that while satisfactory responses are sometimes obtained when high doses are employed the response is not as consistent or predictable as that achieved by parenteral administration. Usually, it is injected subcutaneously or intramuscularly.

#### ABBOTT LABORATORIES

**Solution Bevidox Crystalline:** 10 cc. vials. An isotonic solution containing 30 mcg. of cyanocobalamin in each cubic centimeter. Preserved with 0.01 per cent benzethonium chloride.

U. S. trademark 538,155.

#### THE BIO-RAMO DRUG COMPANY

**Solution Crystalline Rametin with Benzyl Alcohol 1.5%:** 10 cc. vials. A solution containing 10 mcg. of cyanocobalamin in each cubic centimeter.

#### PREMO PHARMACEUTICAL LABORATORIES, INC.

**Solution Crystalline Vitamin B<sub>12</sub>:** 5 cc. and 10 cc. vials. A saline solution containing 50 mcg. of cyanocobalamin in each cubic centimeter. Preserved with 0.5 per cent phenol.

**Solution Crystalline Vitamin B<sub>12</sub>:** 10 cc. vials. A saline solution containing 30 mcg. of cyanocobalamin in each cubic centimeter.

#### RAYMER PHARMACAL COMPANY

**Solution Crystalline Vitamin B<sub>12</sub>:** 10 cc. vials. A saline solution containing 30 or 50 mcg. of cyanocobalamin in each cubic centimeter. Preserved with 0.5 per cent phenol.

#### WILLIAM H. RORER, INC.

**Solution Crystalline Vitamin B<sub>12</sub>:** 1 cc. ampuls. A solution containing 30 mcg. of cyanocobalamin in each cubic centimeter. Buffered with sodium acetate and acetic acid.

**Solution Crystalline Vitamin B<sub>12</sub> with Benzyl Alcohol 1.5%:** 10 cc. vials. A solution containing 30 or 50 mcg. of cyanocobalamin in each cubic centimeter. Buffered with sodium acetate and acetic acid.

#### THE VITARINE COMPANY, INC.

**Solution Crystalline Vitamin B<sub>12</sub> with Benzyl Alcohol 1.5%:** 10 cc. vials. A saline solution containing 30 or 50 mcg. of cyanocobalamin in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**VITAMIN B<sub>12</sub> WITH INTRINSIC FACTOR CONCENTRATE.—**  
**Bifacton (ORGANON).**—A complex prepared from vitamin B<sub>12</sub>



and intrinsic factor concentrate. The latter is prepared from hog stomach.

**Actions and Uses.**—Vitamin B<sub>12</sub>, also known as the extrinsic factor, when combined with intrinsic factor concentrate (a partially purified preparation of the intrinsic factor of Castle obtained from stomach tissue of hogs), is effective orally for the treatment of pernicious anemia with and without neurologic complications. It is also effective by virtue of its vitamin B<sub>12</sub> content in the treatment of tropical and nontropical sprue, nutritional macrocytic anemia caused by vitamin B<sub>12</sub> deficiency and macrocytic anemia of infancy. The intrinsic factor, which is lacking in patients with pernicious anemia, increases the efficiency of alimentary absorption of vitamin B<sub>12</sub>.

Oral administration of vitamin B<sub>12</sub> with intrinsic factor concentrate produces an adequate hematopoietic response in patients with pernicious anemia; therefore, it is suitable to replace injectable cyanocobalamin or liver for patients in whom parenteral therapy is difficult or undesirable. Patients should be observed carefully during oral treatment; if expected improvement does not occur, further examination should be made to rule out complicating disorders, such as infection, gastro-intestinal malfunction or undiagnosed malignant disease. In the presence of any such complication, the dosage may need to be increased or abandoned in favor of injection therapy with cyanocobalamin or liver.

Vitamin B<sub>12</sub> with intrinsic factor concentrate is fairly stable in dry form, but until more is known regarding the keeping qualities of the intrinsic factor, the mixture should be protected from moisture, light and heat above 45°. The mixture has not been reported to produce any toxic effects. The possibility of gastro-intestinal allergy to hog protein, from which the intrinsic factor is derived, should be borne in mind.

**Dosage.**—Vitamin B<sub>12</sub> with intrinsic factor concentrate is administered orally. The potency is expressed in terms of the U.S.P. oral unit of hematopoietic activity, assigned on the basis of clinical assays submitted to the U.S.P. Anti-Anemia Preparations Advisory Board. The declaration of the amount of cyanocobalamin present in preparations of the mixture is excluded to avoid the misleading implication that this represents additional hematopoietic activity in excess of the labeled unitage.

The average daily dosage for the treatment of pernicious and related macrocytic anemias is 1 U.S.P. oral unit daily, in two divided doses of one-half unit each before the morning and evening meals. In severe cases, a more rapid response may be achieved with an initial daily dosage of 2 U.S.P. oral units, also given twice daily in equally divided doses for the first 1 or 2 weeks of therapy. Reticulocyte values usually rise to peak levels within 5 to 12 days. Values for other formed elements of the blood approach normal within 8 to 10 weeks. Megaloblastic bone marrow may return to normal within a few days. Neurologic complications usually are relieved within a period of 1 to 12 weeks, depending on their duration and the intensity of the therapy.



ORGANON, INC.

**Tablets Bifactor:** Each tablet contains the equivalent of one-half U.S.P. oral unit.

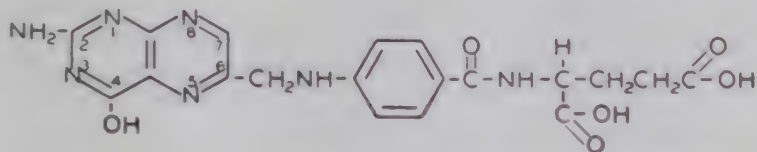
U. S. trademark 566,740.

## Folic Acid

Folic acid, a compound widely distributed in foods, is also known by the chemical name pteroylglutamic acid. Only a small portion of the folic acid found in many foods occurs in the free form and it is not yet clear to what extent the combined forms can be utilized by man. The combined forms differ chemically from free folic acid in that they contain additional molecules of glutamic acid and they may be rendered active after hydrolysis with suitable enzymes or acids.

Although folic acid may restore to normal the blood of patients with pernicious anemia, it should never be used alone in the treatment of this disease because it is ineffective in the control of the neurologic symptoms. The substance is specific in the control of certain megaloblastic anemias of infancy and of pregnancy. It is effective in the treatment of most cases of sprue and nutritional macrocytic anemia.

**FOLIC ACID-U.S.P.—Folvite (LEDERLE).—**Pteroylglutamic acid.—N-[4-{{(2-amino-4-hydroxy-6-pteridyl)methyl}amino}benzoyl] glutamic acid.—“Folic Acid contains not less than 94 per cent of  $C_{19}H_{19}N_7O_6$  calculated to the anhydrous basis.” U.S.P. The structural formula of folic acid may be represented as follows:



**Physical Properties.**—Folic acid is a yellow or yellowish orange, odorless, crystalline powder. It is insoluble in water, alcohol or the usual organic solvents. It is soluble in dilute solutions of alkali hydroxides and their carbonates and is moderately soluble in hot, diluted hydrochloric or sulfuric acid.

**Actions and Uses.**—Folic acid produces a response of the blood, similar to that obtained with liver extract, in pernicious anemia, sprue and nutritional macrocytic anemia in man, and in experimental macrocytic anemias due to dietary deficiencies in monkeys, growing chicks and in fish. It also controls the diarrhea in sprue, but does not prevent or cause improvement in the spinal cord lesions in pernicious anemia; these are helped by liver extract. Therefore, in the treatment of pernicious anemia, folic acid should be used only as an adjunct to treatment with liver or cyanocobalamin.

**Dosage.**—Orally, 5 to 15 mg. daily. Folic acid may be adminis-

tered by intramuscular injection, but in ordinary cases there is no advantage.

**ABBOTT LABORATORIES**

Tablets Folic Acid: 5 mg.

**AMERICAN PHARMACEUTICAL COMPANY, INC.**

Tablets Folic Acid: 5 mg.

**LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY**

Elixir Folvite: 125 cc. bottles. An elixir containing 1.25 mg. of folic acid in each cubic centimeter.

Tablets Folvite: 5 mg.

U. S. patent 2,443,165.

**PHYSICIANS' DRUG & SUPPLY COMPANY**

Tablets Folic Acid: 5 mg.

**PREMO PHARMACEUTICAL LABORATORIES, INC.**

Tablets Folic Acid: 5 mg.

**REXALL DRUG COMPANY**

Tablets Folic Acid: 5 mg.

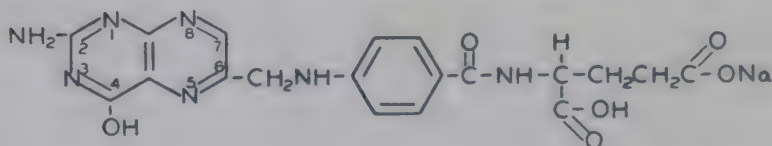
**THE UPJOHN COMPANY**

Tablets Folic Acid: 5 mg.

**WALKER LABORATORIES, INC.**

Tablets Folic Acid: 5 mg. and 10 mg.

**SODIUM FOLATE.**—Sodium Folvite (LEDERLE).—Sodium pteroylglutamate. — Sodium N-[4-{[(2-amino-4-hydroxy-6-pteridyl)methyl]amino}benzoyl]glutamate. — The structural formula of sodium folate may be represented as follows:



**Physical Properties.**—Sodium folate in solution is a clear, mobile yellow to orange-yellow liquid. In a concentration equivalent to 15 mg. of folic acid per milliliter it has a pH between 8.5 and 11.0.

**Actions and Uses.**—Sodium folate possesses the activity of folic acid and is preferred when parenteral therapy is indicated.

**Dosage.**—See the monograph on folic acid.

**LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY**

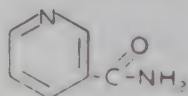
Solution Sodium Folvite: 1 cc. ampuls. A solution containing 15 mg. of sodium folate in each cubic centimeter.

**Solution Sodium Folvite with Benzyl Alcohol 1.5%:** 10 cc. vials. A solution containing 15 mg. of sodium folate in each cubic centimeter.

## Nicotinic Acid and Nicotinamide

Nicotinic acid ( $C_6H_5O_2N$ ) and nicotinamide ( $C_6H_6ON_2$ ) are of fundamental importance in the treatment of pellagra. The terms, niacin and niacinamide, are now officially recognized as synonyms for these chemical names.

**NICOTINAMIDE-U.S.P.**—Nicotinic Acid Amide.—Niacinamide.—“Nicotinamide, dried over sulfuric acid for 4 hours, contains not less than 98.5 per cent of  $C_6H_6N_2O$ .” *U.S.P.* The structural formula of nicotinamide may be represented as follows:



**Physical Properties.**—Nicotinamide occurs as a white, crystalline powder, nearly odorless and of bitter taste. One gram dissolves in about 1 ml. of water, in about 1.5 ml. of alcohol and in about 10 ml. of glycerin, at  $25^\circ$ .

**Actions and Uses.**—See the monograph on nicotinic acid. For parenteral use nicotinamide is preferred to nicotinic acid. Nicotinamide does not produce flushing.

**Dosage.**—See the monograph on nicotinic acid.

### ABBOTT LABORATORIES

**Solution Nicotinamide:** 2 cc. ampuls. A solution containing 50 mg. of nicotinamide in each cubic centimeter.

**Tablets Nicotinamide:** 50 mg. and 100 mg.

### AMERICAN PHARMACEUTICAL COMPANY, INC.

**Tablets Nicotinamide:** 50 mg. and 100 mg.

### BREWER & COMPANY, INC.

**Solution Niacinamide:** 10 cc. vials. A solution containing 100 mg. of nicotinamide in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

### COLE CHEMICAL COMPANY

**Tablets Niacinamide:** 100 mg.

### THE DRUG PRODUCTS COMPANY, INC.

**Pulvoids Nicotinamide:** 50 mg.

**Hyposols Solution Nicotinamide:** 10 cc. vials. A solution containing 50 mg. of nicotinamide in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.



## FLINT, EATON &amp; COMPANY

Tablets Nicotinamide: 50 mg.

## IVES-CAMERON COMPANY, INC.

Tablets Nicotinic Acid Amide: 50 mg. and 100 mg.

## MERCK &amp; COMPANY, INC.

Powder Niacinamide: 25 Gm., 125 Gm., 500 Gm. and 1 Kg. bottles.

## PHYSICIANS' DRUG &amp; SUPPLY COMPANY

Tablets Niacinamide: 50 mg. and 100 mg.

## U. S. VITAMIN CORPORATION

Solution Niacinamide: 2 cc. ampuls. A solution containing 50 mg. of nicotinamide in each cubic centimeter.

Tablets Niacinamide: 25 mg., 50 mg. and 100 mg.

## THE UPJOHN COMPANY

Solution Nicotinic Acid Amide: 1 cc. ampuls and 10 cc. vials. A solution containing 100 mg. of nicotinamide in each cubic centimeter. Preserved with 5 mg. chlorobutanol.

Tablets Nicotinic Acid Amide: 50 mg. and 100 mg.

## THE VALE CHEMICAL COMPANY, INC.

Tablets Nicotinamide: 50 mg.

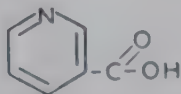
## WALKER LABORATORIES, INC.

Tablets Niacinamide: 25 mg., 50 mg. and 100 mg.

## WARREN-TEED PRODUCTS COMPANY

Tablets Nicotinamide: 50 mg.

**NICOTINIC ACID-U.S.P.**—Niacin.—“Nicotinic Acid, dried at 105° for 1 hour, contains not less than 99.5 per cent of  $C_6H_5NO_2$ .” *U.S.P.* The structural formula of nicotinic acid may be represented as follows:



**Physical Properties.**—Nicotinic acid is a white, odorless, crystalline powder. It is soluble in water, in alcohol and in solutions of alkali carbonates. It occurs in various plant and animal tissues but apparently cannot be synthesized by animals.

**Actions and Uses.**—Nicotinic acid and nicotinamide are recognized as specifics only in the treatment of pellagra. Their administration in appropriate doses leads to the disappearance of all alimentary, dermal and other lesions characteristic of the disease, to a return

to normal of the porphyrin and porphyrinlike pigments of the urine, and to a profound improvement in the mental symptoms which result from inadequate intake of nicotinic acid and nicotinamide. These compounds are without influence upon the polyneuritis so frequently observed in pellagrous patients. In such cases it may be necessary to insure adequate intake of thiamine hydrochloride.

Administration of large doses of nicotinic acid produces flushing of the face and neck sometimes associated with an unpleasant sensation, but the reaction is transient and apparently harmless. The effect is not observed following the administration of nicotinamide.

**Dosage.**—For infants, the recommended intake of nicotinic acid is 4 mg. daily. This recommended intake increases with age to 13 to 17 mg. daily between the ages of 13 and 20. Adults should receive 12 to 18 mg. daily. During pregnancy and lactation, 15 mg. daily is recommended. The dose for therapeutic purposes varies with the severity of the deficiency, and possibly with other as yet unknown factors. The maximum quantity to be recommended is 500 mg. per day, given in ten doses of 50 mg. each.

#### ABBOTT LABORATORIES

Tablets Nicotinic Acid: 50 mg. and 100 mg.

#### AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Nicotinic Acid: 25 mg., 50 mg. and 100 mg.

#### THE BOWMAN BROS. DRUG COMPANY

Tablets Nicotinic Acid: 50 mg.

#### ENDO PRODUCTS, INC.

Tablets Nicotinic Acid: 50 mg. and 100 mg.

#### IVES-CAMERON COMPANY, INC.

Tablets Nicotinic Acid: 25 mg., 50 mg. and 100 mg.

#### MERCK & COMPANY, INC.

Powder Niacin: 25 Gm., 125 Gm. and 500 Gm. bottles.

#### THE WM. S. MERRELL COMPANY

Tablets Nicotinic Acid: 50 mg.

#### NATIONAL DRUG COMPANY

Tablets Nicotinic Acid: 50 mg. and 100 mg.

#### PARKE, DAVIS & COMPANY

Tablets Nicotinic Acid: 50 mg. and 100 mg.

#### PHYSICIANS' DRUG & SUPPLY COMPANY

Tablets Niacin: 25 mg.

#### REXALL DRUG COMPANY

Tablets Nicotinic Acid: 50 mg. and 100 mg.

## U. S. VITAMIN CORPORATION

Tablets Niacin: 25 mg., 50 mg. and 100 mg.

## THE UPJOHN COMPANY

Tablets Nicotinic Acid: 50 mg. and 100 mg.

## THE VALE CHEMICAL COMPANY, INC.

Tablets Niacin: 50 mg.

## WALKER LABORATORIES, INC.

Tablets Nicotinic Acid: 25 mg., 50 mg. and 100 mg.

## WARREN-TEED PRODUCTS COMPANY

Tablets Niacin: 50 mg.

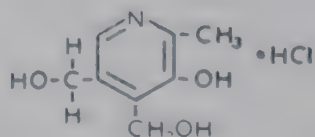
**Pyridoxine**(Vitamin B<sub>6</sub>)

Pyridoxine, pyridoxal and pyridoxamine are naturally-occurring compounds which have the biologic activity attributed to vitamin B<sub>6</sub>. Pyridoxine apparently is converted into pyridoxal, a substance identified as a constituent of an enzyme system which plays a role in the metabolism of amino acids.

In a critical study it was observed that convulsions and hypochromic anemia developed in pyridoxine deficient infants. In another experiment the pyridoxine antagonist desoxypyridoxine was administered to adult subjects while they were maintained on a diet deficient in the vitamins of the B complex. Skin and oral lesions resembling those occurring in riboflavin and niacin deficiency developed. Administration of the vitamin B complex devoid of pyridoxine did not improve the condition but the lesions responded promptly to pyridoxine. The practical significance of these observations has not been determined, since no cases of vitamin B<sub>6</sub> deficiency, other than those produced experimentally, have been described with certainty.

Pyridoxine has some value in the treatment of irradiation sickness. The mechanism of this effect has not been established. Pyridoxine may also be of value in the treatment of nausea of pregnancy, but it is not effective in all cases and should be used only as an adjunct to other control measures.

**PYRIDOXINE HYDROCHLORIDE.**—2-Methyl-3-hydroxy-4,5-di-(hydroxymethyl)pyridine hydrochloride.—Vitamin B<sub>6</sub> hydrochloride.—The structural formula of pyridoxine hydrochloride may be represented as follows:



**Physical Properties.**—Pyridoxine hydrochloride is a white, odor-



less, crystalline powder which melts with decomposition between 200 and 212°. In the crystalline state it is reasonably stable to light and air. Acidic solutions of pyridoxine hydrochloride are stable and may be heated for 30 minutes at 120° without decomposition. One part is soluble in 4.5 parts of water and 100 parts of alcohol; it is sparingly soluble in acetone and practically insoluble in ether. Aqueous solutions are acidic. A solution containing 10 mg. per milliliter has a pH of about 3.

**Actions and Uses.**—Pyridoxine hydrochloride may be of value as an adjunct in the treatment of nausea of pregnancy and in irradiation sickness.

**Dosage.**—There is insufficient information now available with respect to effective dosages of vitamin B<sub>6</sub> to warrant setting up definite dosage recommendations. Quantities ranging from 25 to 100 mg. daily have been used in most of the clinical studies involving nausea and vomiting of pregnancy and irradiation sickness. However, in none of these studies was there an attempt to establish the minimum effective therapeutic dose. Studies with experimental animals show that the requirement for vitamin B<sub>6</sub> is essentially the same as for thiamine. If the human requirement is approximately 1 mg. a day, therapeutic dosages of the order of 5 to 10 mg. daily would be indicated.

#### ABBOTT LABORATORIES

**Solution Pyridoxine Hydrochloride:** 2 cc. ampuls. A solution containing 25 mg. of pyridoxine hydrochloride in each cubic centimeter.

**Tablets Pyridoxine Hydrochloride:** 25 mg. and 50 mg.

#### AMERICAN PHARMACEUTICAL COMPANY

**Tablets Pyridoxine Hydrochloride:** 10 and 25 mg.

#### BREWER & COMPANY, INC.

**Solution Pyridoxine Hydrochloride:** 10 cc. vials. A solution containing 50 mg. of pyridoxine hydrochloride in each cubic centimeter.

#### ENDO PRODUCTS, INC.

**Solution Pyridoxine Hydrochloride:** 1 cc. ampuls. A solution containing 25 mg. or 50 mg. of pyridoxine hydrochloride in each cubic centimeter.

10 cc. vials. A solution containing 50 mg. of pyridoxine hydrochloride in each cubic centimeter.

#### IVES-CAMERON COMPANY, INC.

**Tablets Pyridoxine Hydrochloride:** 25 mg. and 50 mg.

#### LINCOLN LABORATORIES, INC.

**Lyophilized Pyridoxine Hydrochloride:** 10 cc. vials. Each vial contains 0.5 Gm. of pyridoxine hydrochloride. Reconstitution with accompanying diluent gives a solution containing 50 mg. of

pyridoxine hydrochloride in each cubic centimeter. The diluent contains 0.16 per cent methylparaben and 0.04 per cent propylparaben as preservatives.

**MERCK & COMPANY, INC.**

**Powder Pyridoxine Hydrochloride:** 1 Gm., 5 Gm., 25 Gm., 100 Gm. and 500 Gm. bottles and 1 Kg. and 5 Kg. fiber drums for manufacturing use.

U. S. trademark 377,657.

**E. S. MILLER LABORATORIES, INC.**

**Solution Pyridoxine Hydrochloride:** 1 cc. ampuls and 15 cc. vials. A solution containing 50 mg. of pyridoxine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Tablets Pyridoxine Hydrochloride:** 10 mg.

**PHYSICIANS' DRUG & SUPPLY COMPANY**

**Tablets Pyridoxine Hydrochloride:** 5 mg. and 25 mg.

**U. S. VITAMIN CORPORATION**

**Solution Pyridoxine Hydrochloride:** 10 cc. vials. A solution containing 50 mg. of pyridoxine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**Tablets Pyridoxine Hydrochloride:** 25 mg. and 50 mg.

**THE UPJOHN COMPANY**

**Solution Pyridoxine Hydrochloride:** 2 cc. ampuls. A solution containing 50 mg. of pyridoxine hydrochloride in each cubic centimeter.

**Tablets Pyridoxine Hydrochloride:** 10 mg.

**THE VALE CHEMICAL COMPANY, INC.**

**Tablets Pyridoxine Hydrochloride:** 10 mg.

**THE VITARINE COMPANY, INC.**

**Solution Pyridoxine Hydrochloride:** 10 cc. vials. A solution containing 50 mg. of pyridoxine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

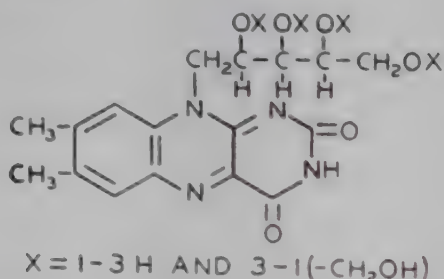
## Riboflavin

(Vitamin B<sub>2</sub>)

Riboflavin, the empirical formula of which is  $C_{17}H_{20}N_4O_6$ , was formerly known as vitamin G, vitamin B<sub>2</sub>, or lactoflavin. The chemical nature of the vitamin was established in 1935.

**METHYLOL RIBOFLAVIN.**—**Hyflavin (ENDO).**—A mixture of methylol derivatives of riboflavin formed by the action of formaldehyde on riboflavin in weakly alkaline solution. The number of methylol groups formed in the ribityl moiety varies from

one to three. The structural formula of methylol riboflavin may be represented as follows:



**Physical Properties.**—Methylol riboflavin is an orange to yellow, hygroscopic powder. It is almost odorless or has a slight odor of formaldehyde. It is soluble in water and practically insoluble in alcohol, benzene, chloroform and ether. It is dextrorotatory. The pH of a 10 per cent solution is between 6.7 and 7.9. The dry powder is unstable. It loses its biological activity in the course of several months with the liberation of formaldehyde and the partial formation of products practically insoluble in water.

**Actions and Uses.**—Methylol riboflavin possesses the activity of riboflavin and is preferable for parenteral therapy.

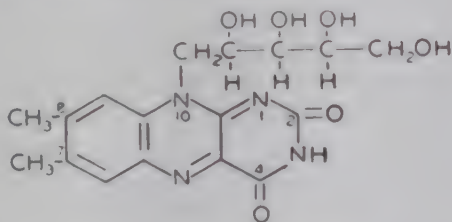
**Dosage.**—See the monograph on riboflavin.

ENDO PRODUCTS, INC.

**Solution Hyflavin with Benzyl Alcohol 2%:** 1 cc. ampuls and 10 cc. vials. A solution containing the equivalent of 10 mg. riboflavin in each cubic centimeter.

U. S. trademark 434,874.

**RIBOFLAVIN-U.S.P.**—Lactoflavin.—Vitamin B<sub>2</sub>.—Vitamin G.—“Riboflavin, dried at 105° for 2 hours, contains not less than 98 per cent of C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O<sub>6</sub>.” U.S.P. The structural formula of riboflavin may be represented as follows:



**Physical Properties.**—Riboflavin occurs as an orange-yellow, crystalline powder of a slight odor. When dry, it is not appreciably affected by diffused light, but in solution, especially in the presence of alkalis, it deteriorates on exposure to light. One gram dissolves in about 10,000 ml. of water at 25° but is more soluble in a physiologic solution of sodium chloride. It is less soluble in alcohol but very soluble in dilute alkalis.

**Actions and Uses.**—Riboflavin is a specific in the treatment of



certain characteristic lesions of the tongue, the lips and the face. The symptoms may be described briefly as follows: A glossitis may be observed before other signs of riboflavin deficiency occur. As the deficiency progresses, the lips become reddened, then shiny and denuded, with maceration and fissuring of the angles of the mouth (cheilosis). Frequently, seborrheic follicular keratoses occur at the nasolabial folds and even over the nose and forehead.

Riboflavin deficiency is responsible for certain ocular manifestations characterized by itching, burning and a sensation of roughness of the eyes (keratitis), accompanied by mild photophobia. The anatomic changes may vary from a superficial invasion of the cornea by capillaries to an extensive vascular proliferation, with or without infiltration, opacity and exudate formation.

Riboflavin may also be used for the alleviation of symptoms of riboflavin deficiency encountered in other diseases, notably pellagra.

**Dosage.**—For infants, the recommended intake of riboflavin is 0.6 mg. daily. The allowance increases to 2 to 2.5 mg. daily between the ages of 13 and 20 years. Adults should ingest 1.5 to 1.8 mg. daily. The requirement during pregnancy and lactation is higher. When riboflavin is used therapeutically the dosage varies from 2 to 10 mg. per day depending upon the severity of the deficiency. No side effects have been noticed following the clinical administration of relatively large doses. The vitamin is equally effective whether administered orally or parenterally.

**ABBOTT LABORATORIES.**

Tablets Riboflavin: 5 mg. and 10 mg.

**AMERICAN PHARMACEUTICAL COMPANY, INC.**

Tablets Riboflavin: 5 mg. and 10 mg.

**ENDO PRODUCTS, INC.**

Tablets Riboflavin: 5 mg.

**HART DRUG CORPORATION**

Tablets Riboflavin: 5 and 10 mg.

**IVES-CAMERON COMPANY, INC.**

Tablets Riboflavin: 5 mg. and 10 mg.

**MERCK & COMPANY, INC.**

Powder Riboflavin: 1 Gm., 5 Gm., 25 Gm. and 100 Gm. bottles.

**PREMO PHARMACEUTICAL LABORATORIES, INC.**

Tablets Riboflavin: 1 mg., 2 mg., 5 mg. and 10 mg.

**PHYSICIANS' DRUG & SUPPLY COMPANY**

Tablets Riboflavin: 2 mg. and 5 mg.

**U. S. VITAMIN CORPORATION**

Tablets Riboflavin: 1 mg. and 5 mg.

## THE UPJOHN COMPANY

Tablets Riboflavin: 5 mg.

## THE VALE CHEMICAL COMPANY, INC.

Tablets Riboflavin: 1 mg. and 5 mg.

## WALKER LABORATORIES, INC.

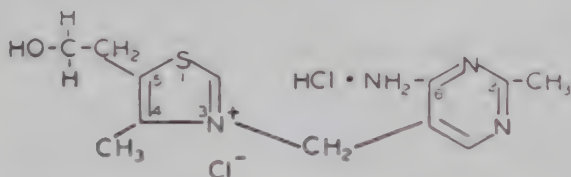
Tablets Riboflavin: 1 mg., 5 mg. and 10 mg.

## Thiamine

(Vitamin B<sub>1</sub>)

This vitamin is of fundamental importance in beriberi. The pure compound was first isolated in 1927. Since that time its chemical constitution has been established and it is now manufactured synthetically. It is usually marketed as the hydrochloride.

**THIAMINE HYDROCHLORIDE-U.S.P.**—Thiamine chloride.—Vitamin B<sub>1</sub> hydrochloride.—Vitamin B<sub>1</sub>.—"Thiamine Hydrochloride, dried at 105° for 2 hours, contains not less than 98 per cent of C<sub>12</sub>H<sub>17</sub>ClN<sub>4</sub>OS.HCl." *U.S.P.* The structural formula of thiamine hydrochloride may be represented as follows:



**Physical Properties.**—Thiamine hydrochloride occurs as small, white crystals or as a crystalline powder, having a slight, characteristic odor. One gram dissolves in about 1 ml. of water and in about 100 ml. of alcohol at 25°. It is soluble in glycerin.

**Actions and Uses.**—Thiamine is of value in correcting and preventing beriberi. This disease with its nervous and cardiovascular manifestations is due primarily to an insufficient supply of thiamine. It is probable that in the majority of instances of human beriberi there are also deficiencies of food constituents other than thiamine. There are conditions which probably could be designated as "latent beriberi"; it does not seem wise at this time to formulate a definite statement covering such conditions other than that below concerning beriberi heart.

Thiamine is of value in correcting and preventing anorexia of dietary origin only if the fault of the diet is lack of thiamine.

The administration of thiamine in excess of that present in the ordinary diet may be advantageous when there are specific conditions indicating interference with proper assimilation of the vitamin. Among these conditions are pernicious vomiting of pregnancy, tube feeding through a jejunal fistula and the like.

While it has not been established that thiamine deficiency is the

sole cause of alcoholic neuritis, the neuritis of pregnancy and the neuritis of pellagra, this vitamin may be of value in the treatment of these conditions.

Thiamine is effective in re-establishing the normal function of the cardiovascular system if the dysfunction was caused by thiamine deficiency. Evidence is lacking that thiamine is effective in any other type of heart disease. At times organic heart disease and beriberi heart coexist. Administration of thiamine is justified in these patients.

Thiamine requirement is increased when there is greatly augmented metabolism such as occurs in febrile conditions, hyperthyroidism or vigorous muscular activity.

**Dosage.**—For infants the recommended daily intake of thiamine hydrochloride is 0.4 mg. The allowance increases to 1.3 to 1.7 mg. daily between the ages of 13 and 20 years. Adults should receive 1 to 1.8 mg. daily. In the well-balanced diet the thiamine requirement should be obtained from the food. Evidence on which to base dosages in the treatment of acute deficiencies is meager. Doses of the order of 10 to 50 mg. may be advantageous in specific instances. Thiamine is rapidly absorbed from the digestive tract and indications for parenteral administration are limited. Intravenous administration is neither necessary nor desirable. Injections of large dosages of highly potent solutions may cause anaphylactic shock.

#### ABBOTT LABORATORIES

Tablets Thiamine Hydrochloride: 3 mg., 5 mg. and 10 mg.

#### AMERICAN PHARMACEUTICAL COMPANY, INC.

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

#### THE BOWMAN BROS. DRUG COMPANY

Tablets Thiamine Hydrochloride: 3 mg., 5 mg. and 10 mg.

#### BOYLE & COMPANY

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

#### COLE CHEMICAL COMPANY

**Solution Thiamine Hydrochloride:** 475 cc. and 3.78 liter bottles. A solution containing 0.5 and 1 mg. of thiamine hydrochloride in each cubic centimeter.

Tablets Thiamine Hydrochloride: 1 mg., 3 mg. and 5 mg.

#### THE DRUG PRODUCTS COMPANY, INC.

Pulvoids Thiamine Hydrochloride: 1 mg. and 3 mg.

**Solution Thiamine Hydrochloride:** 1 cc. ampul hyposols. A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter.

10 cc. hyposol vials. A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.



## R. E. DWIGHT &amp; COMPANY

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

## ENDO PRODUCTS, INC.

Solution Thiamine Hydrochloride: 1 cc. ampuls and 10 cc. vials. A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Thiamine Hydrochloride: 1 mg., 3 mg. and 5 mg.

## ENDOCRINE COMPANY

Solution Thiamine Hydrochloride Drops (*Oral*): 30 cc. and 118.3 cc. bottles. A solution containing 50 mg. of thiamine hydrochloride in each cubic centimeter.

## FLINT, EATON &amp; COMPANY

Solution Thiamine Hydrochloride: 1 cc. ampuls. A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter.

Tablets Thiamine Hydrochloride: 1 mg., 5 mg. and 10 mg.

## GOLD LEAF PHARMACAL COMPANY

Solution Thiamine Hydrochloride: 10 cc. vials. A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

Tablets Thiamine Hydrochloride: 1 mg., 5 mg. and 10 mg.

## HORTON &amp; CONVERSE

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

## IVES-CAMERON COMPANY, INC.

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

## LINCOLN LABORATORIES, INC.

Lyophilized Thiamine Hydrochloride: 10 cc. vials. Each vial contains 0.1 Gm. of thiamine hydrochloride. Reconstitution with accompanying diluent gives a solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter. The diluent contains 0.16 per cent methylparaben and 0.04 per cent propylparaben as preservatives.

Tablets Thiamine Hydrochloride: 10 mg.

## McKESSON &amp; ROBBINS, INC.

Tablets Thiamine Hydrochloride: 0.5 mg., 1 mg. and 3 mg.

## MERCK &amp; COMPANY, INC.

Powder Thiamine Hydrochloride: 5 Gm., 25 Gm. and 100 Gm. bottles.

## THE WM. S. MERRELL COMPANY

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

**E. S. MILLER LABORATORIES, INC.**

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

**NATIONAL DRUG COMPANY**

Tablets Thiamine Hydrochloride: 1 mg.

**NION CORPORATION**

Tablets Thiamine Hydrochloride: 10 mg.

**PASADENA RESEARCH LABORATORIES, INC.**

Solution Thiamine Hydrochloride: 10 cc. vials. A solution containing 10 mg. of thiamine hydrochloride in each cubic centimeter. Preserved with 0.35 per cent chlorobutanol.

**PHYSICIANS' DRUG & SUPPLY COMPANY**

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

**WILLIAM H. RORER, INC.**

Tablets Thiamine Hydrochloride: 5 mg.

**E. R. SQUIBB & SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION**

Tablets Thiamine Hydrochloride: 3 mg., 5 mg. and 10 mg.

**SUTLIFF & CASE COMPANY, INC.**

Tablets Thiamine Hydrochloride: 1 mg.

**U. S. VITAMIN CORPORATION**

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

**THE UPJOHN COMPANY**

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

**THE VALE CHEMICAL COMPANY, INC.**

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

**VANPELT & BROWN, INC.**

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

**WALKER LABORATORIES, INC.**

Solution Thiamine Hydrochloride (*Oral*): 15 cc. and 60 cc. bottles. A solution containing 5 mg. of thiamine hydrochloride in each cubic centimeter. Preserved with 0.1 per cent methylparaben.

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg. and 10 mg.

**WINTHROP-STEARNs, INC.**

Tablets Thiamine Hydrochloride: 5 mg. and 10 mg.

**Mixed Vitamin B Components**

**TRIASYN B-U.S.P.**—"Triasyn B Capsules [and Tablets] contain in each capsule [or tablet] not less than 2 mg. of thiamine hydro-

chloride, 3 mg. of riboflavin and 20 mg. of nicotinamide." *U.S.P.*

**Actions, Uses and Dosage.**—For prophylaxis and treatment of conditions arising from deficiency of thiamine, riboflavin and nicotinic acid. See the monographs on these components.

BREWER & COMPANY, INC.

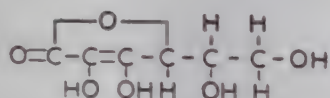
**Gel-ets Triasyn B:** Each capsule contains 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg. of nicotinamide.

## VITAMIN C

Inadequate intakes of vitamin C result in the development of scurvy.

All pure vitamin C used in pharmaceutical products is prepared synthetically.

**ASCORBIC ACID-U.S.P.**—**Cebione (MERCK).**—**Cevex (WALKER VITAMIN).**—**Vitamin C.**—"Ascorbic Acid, dried in a vacuum desiccator over sulfuric acid for 3 hours, contains not less than 99 per cent of  $C_6H_8O_6$ ." *U.S.P.* The structural formula of ascorbic acid may be represented as follows:



**Physical Properties.**—Ascorbic acid is a white, odorless, crystalline powder. It is soluble in water and alcohol. Ascorbic acid in pure dry form is quite stable; but when mixed with other ingredients, either in dry form or in solution, and in many natural products, the vitamin oxidizes on exposure to air or light, and such products should be preserved in an oxygen-free atmosphere protected from light. The international unit for ascorbic acid is defined as the activity of 0.05 mg. of ascorbic acid, but quantities are now almost universally expressed in milligrams.

**Actions and Uses.**—The vitamin is present in such foods as fresh vegetables and fruits, yet entirely lacking in such others as the common cereals and grains.

Ascorbic acid is of therapeutic value for the correction and prevention of scurvy.

It may be permissible under certain conditions to use ascorbic acid in early and latent scurvy. The diagnosis rests, however, on roentgenologic evidences in the long bones, the blood level of ascorbic acid and the clinical picture and history.

Dental caries, pyorrhea, certain gum infections, anorexia, anemia, undernutrition and infection alone are not in themselves sufficient indications of ascorbic acid deficiency but some of these may be concomitant signs of ascorbic acid deficiency. Ascorbic acid is of value in these symptomatic conditions *only when* they are the consequences of a deficiency of ascorbic acid or when there is a pathologic interference with assimilation of the amount necessary for the preservation of health. This latter situation is rare.



Because ascorbic acid is a dietary essential its administration in concentrated form is of value in conditions where difficulty is encountered in introducing it orally or in utilizing ordinary foods in the usual way. It is generally administered in the form of an ascorbic-acid-carrying juice. It may be administered intramuscularly in concentrated form as sodium ascorbate when persistent vomiting, diarrhea or other conditions prevent the utilization of proper amounts taken orally.

In planning diets for infants who do not receive breast milk, and for small children, it is advisable to make special provision for a source of ascorbic acid such as orange juice because the concentration of ascorbic acid in fresh cow's milk is only about one-fourth of the concentration in mother's milk and because in most foods the vitamin content is reduced during cooking or processing.

**Dosage.**—The recommended daily intake of ascorbic acid for an infant is approximately 30 mg. Recommended levels of intake increase through childhood to 80 to 100 mg. daily between the ages of 13 and 20 years. For adults, the recommended daily intake is 70 to 75 mg. During pregnancy and lactation, the allowance may be as high as 100 or 150 mg.

When pharmaceutical preparations are prescribed, the protective dose for infants is 10 mg. daily, and the therapeutic dose is 30 to 50 mg. daily. The protective dose for adults is 25 mg. daily and the therapeutic dose is 100 to 150 mg. daily. Each 1 mg. is equivalent to 20 international units of vitamin C. No evidence exists that tenfold increases exert detrimental effects.

**ABBOTT LABORATORIES**

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

**AMERICAN PHARMACEUTICAL COMPANY, INC.**

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

**THE BOWMAN BROS. DRUG COMPANY**

Tablets Ascorbic Acid: 50 mg. and 100 mg.

**BOYLE & COMPANY**

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

**GEORGE A. BREON & COMPANY, INC.**

Tablets Ascorbic Acid: 100 mg.

**BUFFINGTON'S INC.**

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

**COLE CHEMICAL COMPANY**

Tablets Ascorbic Acid: 25 mg. and 100 mg.

**R. E. DWIGHT & COMPANY**

Tablets Ascorbic Acid: 50 mg. and 100 mg.

**ENDO PRODUCTS, INC.**

Tablets Ascorbic Acid: 10 mg., 25 mg., 50 mg. and 100 mg.

## GOLD LEAF PHARMACAL COMPANY, INC.

Tablets Ascorbic Acid: 50 mg. and 100 mg.

## IVES-CAMERON COMPANY, INC.

Tablets Ascorbic Acid: 50 mg. and 100 mg.

## McKESSON &amp; ROBBINS, INC.

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## MEAD JOHNSON &amp; COMPANY

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## MERCK &amp; COMPANY, INC.

Crystals Cebione: 1 Gm. bottles.

U. S. trademark 318,171.

## THE WM. S. MERRELL COMPANY

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## E. S. MILLER LABORATORIES, INC.

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## NATIONAL DRUG COMPANY

Tablets Ascorbic Acid: 100 mg.

## PHYSICIANS' DRUG &amp; SUPPLY COMPANY

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## PREMO PHARMACEUTICAL LABORATORIES, INC.

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## REXALL DRUG COMPANY

Tablets Ascorbic Acid: 25 and 50 mg.

## SHERMAN LABORATORIES

Tablets Ascorbic Acid: 100 mg.

## E. R. SQUIBB &amp; SONS, DIVISION OF MATHIESON CHEMICAL CORPORATION

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## STANDARD PHARMACEUTICAL COMPANY, INC.

Tablets Ascorbic Acid: 25, 50 and 100 mg.

## SUTLIFF &amp; CASE COMPANY, INC.

Tablets Ascorbic Acid: 50 mg. and 100 mg.

## THE STUART COMPANY

Tablets Ascorbic Acid: 100 mg.

## TABLEROCK LABORATORIES

Tablets Ascorbic Acid: 50 mg.

## U. S. VITAMIN CORPORATION

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## THE UPJOHN COMPANY

Tablets Ascorbic Acid: 25 mg., 50 mg. and 100 mg.

## THE VALE CHEMICAL COMPANY, INC.

Tablets Ascorbic Acid: 25 mg. and 100 mg.

## WALKER LABORATORIES, INC.

Cevex Drops: 15 cc. bottles with dropper. Each cubic centimeter contains 150 mg. of ascorbic acid.

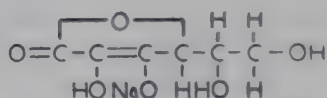
Tablets Cevex: 25 mg., 50 mg. and 100 mg.

U. S. trademark 358,180.

## WINTHROP-STEARNES, INC.

Tablets Ascorbic Acid: 100 mg.

**SODIUM ASCORBATE.**—The sodium salt of vitamin C. The structural formula of sodium ascorbate may be represented as follows:



**Actions and Uses.**—Sodium ascorbate possesses the activity of ascorbic acid and is preferred when intramuscular therapy is indicated. See the monograph on ascorbic acid.

**Dosage.**—See the monograph on ascorbic acid.

## BARRY LABORATORIES, INC.

**Solution Sodium Ascorbate:** 2 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter.

## ENDO PRODUCTS, INC.

**Solution Sodium Ascorbate:** 2 cc. and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. and 100 mg., respectively, of ascorbic acid in each cubic centimeter. Stabilized with the equivalent of 0.08 per cent sulurous acid.

## CARLO ERBA, INC.

**Solution Sodium Ascorbate with Benzyl Alcohol 1%:** 2 cc. and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. and 100 mg., respectively, of ascorbic acid in each cubic centimeter.

## GOLD LEAF PHARMACAL COMPANY, INC.

**Solution Sodium Ascorbate:** 2 cc. and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg.



and 100 mg., respectively, of ascorbic acid in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol and 0.1 per cent sodium bisulfite.

#### KREMERS-URBAN COMPANY

**Solution Sodium Ascorbate:** 2 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter.

#### LINCOLN LABORATORIES, INC.

**Solution Sodium Ascorbate:** 2 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 100 mg. of ascorbic acid in each cubic centimeter.

#### THE WM. S. MERRELL COMPANY

**Solution Sodium Ascorbate:** 2 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter.

#### MEYER CHEMICAL COMPANY

**Solution Sodium Ascorbate:** 2 cc. ampuls. A solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter. Stabilized with 0.1 per cent sodium bisulfite and 0.1 per cent cysteine hydrochloride.

2 cc. and 5 cc. ampuls. A solution containing sodium ascorbate equivalent to 0.1 Gm. of ascorbic acid in each cubic centimeter. Stabilized with 0.1 per cent cysteine hydrochloride and 0.1 per cent sodium bisulfite.

#### PARKE, DAVIS & COMPANY

**Solution Sodium Ascorbate:** 2 cc. Glaseptic ampuls. A solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter. Preserved with 0.1 per cent sodium bisulfite.

#### WILLIAM H. RORER, INC.

**Solution Sodium Ascorbate:** 1 cc. and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 0.1 Gm. of ascorbic acid in each cubic centimeter. Preserved with 0.01 per cent aminoacetic acid.

#### STANDARD PHARMACEUTICAL COMPANY, INC.

**Solution Sodium Ascorbate:** 2 cc. and 5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. and 100 mg., respectively, of ascorbic acid in each cubic centimeter. Preserved with 0.4 per cent chlorobutanol and 0.2 per cent sodium bisulfite.

#### TESTAGAR & COMPANY

**Solution Sodium Ascorbate:** 2 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 50 mg. of ascorbic

acid in each cubic centimeter. Preserved with 0.18 per cent methylparaben and 0.02 per cent propylparaben.

5 cc. ampuls. A sterile aqueous solution containing sodium ascorbate equivalent to 100 mg. of ascorbic acid in each cubic centimeter. Preserved with 0.35 per cent chlorobutanol.

#### THE VITARINE COMPANY

**Solution Sodium Ascorbate:** 2 cc. ampuls. A solution containing sodium ascorbate equivalent to 50 mg. of ascorbic acid in each cubic centimeter.

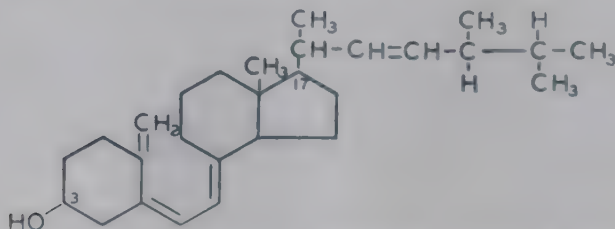
5 and 10 cc. ampuls. A solution containing sodium ascorbate equivalent to 100 mg. of ascorbic acid in each cubic centimeter. All sizes preserved with 0.1 per cent sodium bisulfite and 0.5 per cent chlorobutanol.

## VITAMIN D

The term "vitamin D" is applied to two or more substances which have a function in the proper utilization of calcium and phosphorus. Two forms of naturally occurring vitamin D have been isolated. One of these, vitamin D<sub>2</sub>, or calciferol, is obtained in pure crystalline form as one of the products of the ultraviolet irradiation of ergosterol, the other, vitamin D<sub>3</sub>, can be prepared in the same manner from 7-dehydrocholesterol. Antirachitic activation of these compounds can also be accomplished by electronic bombardment. These two forms of vitamin D possess equal antirachitic potency in man. They also tend to elevate the level of serum calcium, an effect which varies with the different substances and does not parallel the antirachitic effect.

**CALCIFEROL-U.S.P. — Drisdol (WINTHROP-STEARNES).** — Vitamin D<sub>2</sub>.—9,10-Ergostatetraene-(18:10, 5:6, 7:8, 22:23)-ol-3.

Vitamin D<sub>2</sub> may be prepared by ultraviolet irradiation of ergosterol in a suitable solvent or by electronic bombardment of the compound: It is not identical with the vitamin D which predominates in fish liver oils and which is called vitamin D<sub>3</sub>. A method of preparation of vitamin D<sub>2</sub> is given in Addendum 1936 to the British Pharmacopeia, 1932, page 20. The crystals have a potency of 40 units of vitamin D (U.S.P.) per microgram. (For methods of assay see U.S.P. XIV, p. 792.) The structural formula of vitamin D<sub>2</sub> may be represented as follows:



**Physical Properties.**—Calciferol occurs as white, odorless crystals. It is affected by air and by light. Calciferol is insoluble in water.

It is soluble in alcohol, in chloroform, in ether and in fatty oils.

**Actions and Uses.**—Vitamin D is a specific in the prevention and cure of infantile rickets, spasmophilia (infantile tetany) and osteomalacia, diseases which are manifestations of abnormal calcium and phosphorus metabolism. Complications such as renal insufficiency or glandular malfunction may preclude normal response to vitamin D therapy. During acute infections, especially infections of the gastro-intestinal tract, vitamin D may prove ineffective because it is poorly absorbed. Animal experimentation has shown that correction of an inadequate intake of vitamin D results in the more economical utilization of calcium and phosphorus and also that the undesirable effects of improper ratios of calcium and phosphorus in the diet can largely be overcome by a normal intake of vitamin D. The application of these observations to man is not entirely apparent because adequate clinical evidence showing the availability of different forms of calcium and phosphorus is lacking, but it is certain that vitamin D has a favorable influence on the metabolism of calcium and phosphorus.

Vitamin D also plays an important role in tooth formation. It is beneficial in preventing and arresting dental caries when the intake of calcium and phosphorus is liberal and the diet is adequate with respect to other nutrients. Vitamin D is not the only important factor in the prevention or arrest of caries.

Direct exposure of the skin to ultraviolet rays from the sun or from artificial sources results in the formation of vitamin D within the organism but vitamin D does not have all the beneficial effects of exposure to sunshine.

The use of massive doses of vitamin D has been suggested in the treatment of refractory rickets, that is, occasional cases of rickets which do not respond to treatment with the usual dosages or even much larger dosages of vitamin D. In some of these cases the rickets is caused by a disturbance of the acid-base balance and has been successfully treated by administration of sodium bicarbonate or a sodium citrate-citric acid mixture. Massive doses of vitamin D also have proved effective in the control of other cases of rickets. The quantity of vitamin D needed may be so large that it borders on the dosages of vitamin D that are definitely toxic, and such treatment should not be undertaken without first exploring other possibilities or without careful observation for signs of toxicity. Some investigators believe it desirable to examine the urine daily for calcium casts, albumin and red blood cells while the maintenance dose is being established. Others believe less frequent examination is necessary. After the dose is established, weekly examination, using the Sulkowitch test for excessive excretion of calcium, is sufficient. The blood should be examined weekly or oftener to avoid a rise of calcium above 12 mg. per 100 cc. if the dosage exceeds 20,000 units daily for the infant or 50,000 units for a child. If anorexia or nausea should appear, the child must be brought promptly to the attention of the physician and vitamin D administration should be discontinued. When the maintenance dose has been established, operative procedures to correct rachitic deformities may precipitate a temporary state of



toxicity and the blood levels of calcium must be watched closely.

Vitamin D<sub>2</sub> (calciferol) and dihydrotachysterol, when administered in large doses, raise the level of serum calcium. This result is achieved in part by an increased absorption of calcium, and in part by mobilization of calcium from the bones. For this purpose these compounds may be given by mouth over considerable periods, provided the serum calcium does not rise above normal levels. An abnormally high level of calcium in the serum may have a serious or even fatal effect. There is no development of tolerance.

Because of its effect on the level of serum calcium, vitamin D is used in correcting hypocalcemia or parathyroid tetany. Vitamin D<sub>2</sub> and dihydrotachysterol have similar effects and are equally effective in the management of hypoparathyroidism. During their use frequent determinations of serum calcium are desirable. The Sulko-witch test is helpful and is so simple that it may be performed by the patient. Its routine use during treatment reduces the number of determinations of serum calcium which are necessary.

Large doses of vitamin D are of value in the treatment of lupus vulgaris. Clinical evidence does not warrant the use of massive doses of vitamin D in chronic arthritis, allergic disorders or psoriasis.

**Dosage.**—The vitamin D requirement apparently bears no relationship to the age of the individual. A daily intake of 400 units is believed to meet the ordinary requirements of all age groups. In treatment of the average case of rickets, 1,200 to 1,500 units daily appear to suffice. For massive dose therapy in refractory rickets, see the actions and uses statement.

Treatment of parathyroid insufficiency is commonly initiated with relatively large doses of the activated sterols, followed by smaller maintenance doses. The management of acute parathyroid tetany may require 2 to 8 mg. of pure dihydrotachysterol which is approximately equivalent to 10 to 40 mg. or 400,000 to 1,600,000 international units of vitamin D. The amount of the substances necessary for daily maintenance varies greatly in individual cases but averages between 0.6 and 1 mg. of pure dihydrotachysterol or 3 to 5 mg. (120,000 to 200,000 I.U.) of vitamin D.

In recent years there have been reports of the successful use of large doses of vitamin D in the treatment of lupus vulgaris. The most effective dose of the vitamin in the treatment of this condition remains to be determined. Doses of the order of 100,000 to 200,000 units three times during the first week, twice during the second week and weekly thereafter have been used with apparent success. Precautions to avoid injury from excessive intakes of vitamin D should be observed as described in the actions and uses statement.

#### WINTHROP-STEARNs, INC.

Capsules Drisdol Concentrated Solution in Oil: 0.2 cc. Each capsule contains 1.25 mg. of calciferol and has a potency of 50,000 units of vitamin D (U.S.P.).

**Solution Drisdol in Propylene Glycol:** 5 cc., 10 cc. and 50 cc. bottles. Each cubic centimeter contains 0.25 mg. of calciferol and has a potency of 10,000 units of vitamin D (U.S.P.) per gram. The propylene glycol used in the preparation of this product complies with the standards for propylene glycol-N.N.R.

**Capsules Drisdol with Vitamin A:** 5,000 U.S.P. units of vitamin A and 1,000 U.S.P. units of vitamin D in corn oil.

**Solution Drisdol with Vitamin A (*Water Dispersible*):** 10 cc. and 50 cc. bottles. 50,000 U.S.P. units of vitamin A and 10,000 U.S.P. units of vitamin D per gram in sesame oil.

U. S. trademark 333,661.

## VITAMIN E

In 1925 it was demonstrated conclusively that vitamin E must be included in the diet of the rat to insure successful reproduction. There are at least three naturally occurring compounds which have vitamin E activity: alpha, beta and gamma tocopherol. The role of vitamin E in human physiology has not been determined. There seems to be agreement that the vitamin is of no value in the treatment of sterility and of dubious value in the treatment of habitual abortion.

It has been claimed that vitamin E is of value in the treatment of many common, serious diseases. Carefully controlled experiments have not substantiated these claims.

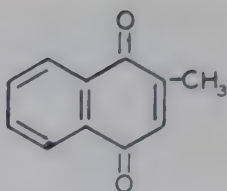
## VITAMIN K

Prolonged clotting time of the blood associated with hypoprothrombinemia results from an inadequate intake of vitamin K or interference with its absorption. This condition responds promptly to proper administration of the vitamin. Investigations have shown that there are at least two naturally occurring substances having a naphthoquinone nucleus which have similar physiologic properties; they are referred to as vitamin  $K_1$ — $C_{31}H_{46}O_2$ —and vitamin  $K_2$ — $C_{41}H_{56}O_2$ .

A number of synthetic naphthoquinone derivatives, referred to as vitamin K analogues, produce a wide range of vitamin K activity, some being even more potent than pure vitamin  $K_1$  or vitamin  $K_2$ . Some of them are water soluble.

Vitamin K alleviates prothrombin deficiency resulting from impaired absorption of the factor from the gut.

**MENADIONE-U.S.P.** — 2-Methyl-1,4-naphthoquinone. — “Menadione, dried over sulfuric acid for 4 hours, contains not less than 98.5 per cent of  $C_{11}H_8O_2$ .” U.S.P. The structural formula of menadione may be represented as follows:



**Physical Properties.**—Menadione is a bright yellow, crystalline powder. It is nearly odorless and is affected by sunlight. It is practically insoluble in water. One gram dissolves in about 60 ml. of alcohol. It is soluble in vegetable oils.

**Actions and Uses.**—Menadione is a synthetic naphthoquinone derivative having the physiologic properties of vitamin K.

Menadione is extraordinarily effective against the hemorrhagic diathesis of obstructive jaundice. Some fat-soluble vitamins, including vitamin K, are not absorbed when the flow of the bile is obstructed, and the liver does not synthesize prothrombin unless vitamin K is available. Thus, prothrombin deficiency in the blood of man may result from this interference with the absorption of vitamin K. When prothrombin deficiency is due to bile obstruction and the vitamin is given orally, to make vitamin K available it is necessary to administer bile salts with vitamin K. The use of certain water-soluble preparations obviates the necessity for concurrent administration of bile salts.

The hemorrhagic state associated with primary hepatic disease is but poorly controlled by vitamin K and its analogues. The efficiency of this treatment is limited because in the formation of prothrombin the liver can utilize the administered vitamin only to a limited extent.

The hemorrhagic states which exist in connection with certain intestinal diseases such as ulcerative colitis, sprue and celiac diseases, characterized by either a loss of continuity of the intestinal tract or by a disturbance of its absorptive surface, are also specifically affected by vitamin K.

In the treatment of the physiologic hypoprothrombinemia of the newborn, which exists during the first week of life, and in the prevention of the consequent hemorrhage, the vitamin and its analogues are specific. As little as 0.5 to 2 mg. of the vitamin or the naphthoquinones, when administered parenterally to a woman during labor, insures that the newborn infant will have a normal amount of prothrombin in the circulating blood. The same doses given parenterally to the newborn infant also produce this effect.

The administration of vitamin K is also effective in the rare cases of primary dietary deficiency of vitamin K.

**Dosage.**—Therapeutic dosage: 1 to 2 mg. daily or as prescribed by the physician. In cases of prothrombin deficiency due to bile obstruction, bile salts should be administered with menadione.

**Caution.**—Menadione powder is irritating to the respiratory tract and to the skin, and an alcoholic solution has vesicant properties."



**R. E. DWIGHT & COMPANY**

**Capsules Menadione: 2 mg.**

**ENDO PRODUCTS, INC.**

**Solution Menadione in Oil:** 2 cc. ampuls. A solution in corn oil containing 1 mg. of menadione in each cubic centimeter.

**Tablets Menadione: 1 mg. and 2 mg.**

**LINCOLN LABORATORIES, INC.**

**Solution Menadione in Oil with Benzyl Alcohol 2%:** 15 cc. vials. A solution in sesame oil containing 2 mg. of menadione in each cubic centimeter. Preserved with 0.5 per cent chlorobutanol.

**E. S. MILLER LABORATORIES, INC.**

**Solution Menadione in Oil:** 1 cc. ampuls. A solution containing 1 mg. of menadione with 2 per cent benzocaine in each cubic centimeter. Preserved with 0.5 per cent cresol.

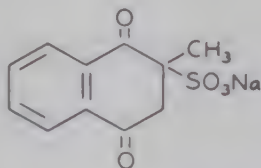
**Tablets Menadione: 1 mg.**

**U. S. VITAMIN CORPORATION**

**Capsules Menadione: 1 mg. and 2 mg.**

**Solution Menadione in Oil:** 1 cc. ampuls. A solution in corn oil containing 1 mg. of menadione in each cubic centimeter.

**MENADIONE SODIUM BISULFITE-U.S.P.—Hykinone (ABBOTT).—Menadione Bisulfite.**—"Menadione Sodium Bisulfite contains not less than 94 per cent of  $C_{11}H_8O_2 \cdot NaHSO_3$ , calculated on the anhydrous basis." *U.S.P.* It may be prepared by the interaction of menadione and sodium bisulfite to form the addition product. The structural formula of menadione sodium bisulfite may be represented as follows:



**Physical Properties.**—Menadione sodium bisulfite occurs as a white, crystalline, odorless hygroscopic powder. One gram of menadione sodium bisulfite dissolves in about 2 ml. of water. It is slightly soluble in alcohol and is almost insoluble in ether and in benzene.

**Actions and Uses.**—Menadione sodium bisulfite is used for the same conditions as is menadione, which possesses the physiologic properties of vitamin K. Unlike menadione it is soluble in water, and stable aqueous solutions may be prepared. Since this material is water soluble, it is effectively administered orally without the use of bile salts in conditions where the flow of bile is obstructed.

**Dosage.**—It may be administered subcutaneously, intramuscularly or intravenously, the average daily dose being 0.5 to 2 mg. During administration of the drug the prothrombin level of the blood should be followed, especially when there appears to be need of an additional dose during a 24-hour period. In patients under treatment with bishydroxycoumarin, if prothrombin activity drops below 15 per cent or signs of bleeding appear, 50 to 100 mg. of menadione sodium bisulfite are given by slow intravenous injection.

#### ABBOTT LABORATORIES

**Solution Hykinone:** 10 cc. ampuls. An isotonic sodium chloride solution containing 7.2 mg. of menadione sodium bisulfite in each cubic centimeter. Stabilized with 0.36 per cent sodium bisulfite.

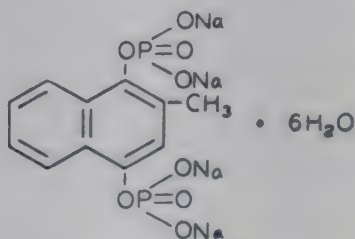
U. S. patent 2,367,302. U. S. trademark 514,207.

#### THE WM. S. MERRELL COMPANY

**Solution Menadione Sodium Bisulfite:** 1 cc. ampuls. A solution containing 3.84 mg. of menadione sodium bisulfite in each cubic centimeter. Stabilized with 0.14 per cent sodium bisulfite.

U. S. patent 2,331,808.

**SODIUM MENADIOL DIPHOSPHATE.**—Synkayvite Sodium Diphosphate (HOFFMANN-LA ROCHE).—The hexahydrate of the tetrasodium salt of 2-methyl-1,4-naphthalenediol diphosphate.—The structural formula of sodium menadiol diphosphate may be represented as follows:



**Physical Properties.**—Sodium menadiol diphosphate is a white or pink to light brown hygroscopic powder with a characteristic odor. It is very soluble in water and insoluble in alcohol and ether. The pH of a 1 per cent solution is 7.8 to 8.5.

**Actions and Uses.**—Sodium menadiol diphosphate, a dihydro derivative of menadione, has the same actions and uses as other analogues of vitamin K. It is therefore useful in the prevention and treatment of hemorrhagic disorders associated with hypoprothrombinemia caused by a deficiency of vitamin K, overdosage of systemic anticoagulants such as bishydroxycoumarin, or secondary to the administration of large doses or the prolonged use of salicylates, quinine, sulfonamides, arsenicals and barbiturates. It is also indicated in physiologic hypoprothrombinemia of the newborn as well as in prothrombin deficiency caused by gastro-intestinal disorders which interfere with the absorption of the vitamin, including deficiency of intestinal bile that is essential for the absorption of natural and fat soluble forms of Vitamin K. Sodium menadiol

diphosphate is water soluble and therefore absorbed following oral administration without bile salts. It is also effective by parenteral administration.

**Dosage.**—Sodium menadiol diphosphate is administered orally and by injection subcutaneously, intramuscularly or intravenously. On the basis of molecular weights, the dosage should be at least three times that of menadione to provide a theoretically equivalent amount of vitamin K activity. The calculated ratio is 3.1 mg. of sodium menadiol diphosphate to 1 mg. of menadione. For the management of prothrombin deficient hemorrhagic states, the average dose for adults should range from 3 to 6 mg. daily and may be administered orally or parenterally as the situation requires. Larger doses may be given if necessary. As an antidote for bishydroxycoumarin overdosage, a dose of 75 mg. intramuscularly, repeated as often as necessary, is recommended. For the prevention of hemorrhage associated with prothrombin deficiency caused by salicylates after tonsillectomy, a total daily dosage of 10 to 25 mg. (administered in three divided doses) is recommended. For the prevention of hemorrhagic disease of the newborn, either 6 to 12 mg. is administered parenterally to the mother during labor, or 3 mg. is given to the infant immediately after delivery.

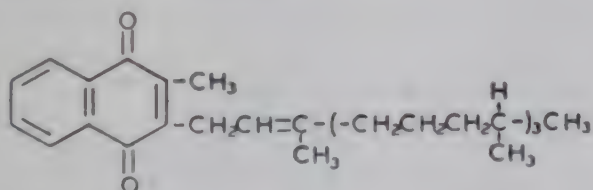
#### HOFFMANN-LAROCHE, INC.

**Solution Synkayvite Sodium Diphosphate:** 1 cc. ampuls. An isotonic solution containing 5 mg. or 10 mg. of sodium menadiol diphosphate in each cubic centimeter. 2 cc. ampuls. An isotonic solution containing 37.5 mg. of sodium menadiol diphosphate in each cubic centimeter. Stabilized with sodium metabisulfite and preserved with 0.45 per cent phenol.

**Tablets Synkayvite Sodium Diphosphate:** 5 mg.

U. S. patent 2,354,132. U. S. trademark 393,117.

**VITAMIN K<sub>1</sub>.**—Mephyton (SHARP & DOHME).—2-Methyl-3-phytyl-1,4-naphthoquinone.—May be isolated from natural sources or be prepared by condensing 2-methyl-1,4-naphthoquinone with the suitable phytyl derivative. The structural formula of vitamin K<sub>1</sub> may be represented as follows:



**Physical Properties.**—Vitamin K<sub>1</sub> is a yellow, very viscous, nearly odorless liquid. It is stable in air but decomposes in sunlight. It is soluble in alcohol, benzene, chloroform, ether and vegetable oils and insoluble in water. A solution of 1 part vitamin K<sub>1</sub> and 20 parts alcohol is neutral to litmus.



**Actions and Uses.**—See the monograph on menadione. Vitamin K<sub>1</sub> has a more prolonged effect than menadione. Vitamin K<sub>1</sub> is more effective than any of the vitamin K analogues in reversing the hypoprothrombinemia induced by bishydroxycoumarin (Dicumarol) and similar anticoagulant agents, and the emulsified preparation is designed for intravenous use in treating this condition.

**Dosage.**—In obstructive jaundice, 4 to 10 mg. by mouth, with or without bile salts. The intravenous dose for adults may be as much as 10 mg. dispersed in dextrose solution. In counteracting anticoagulants, 50 to 150 mg. of emulsified vitamin K<sub>1</sub> intravenously, at a rate not exceeding 10 mg. of vitamin K<sub>1</sub> per minute. Also see the monograph on menadione.

SHARP & DOHME, DIVISION OF MERCK & COMPANY, INC.

**Emulsion Mephyton:** 1 cc. ampuls. An emulsion containing 50 mg. of vitamin K<sub>1</sub> in each cubic centimeter.

## MIXED VITAMINS

### Preparations of Vitamins A and D

Concentrates from fish liver oils and concentrates of vitamin D are used in the manufacture of a variety of vitamin A and D preparations that are used therapeutically and prophylactically. For actions, uses and dosage of vitamins A and D, see monographs on oleovitamin A and calciferol.

**BURBOT LIVER OIL.**—The oil extracted from the livers of the Burbot (*Lota maculosa*), family Gadidae. It has a potency of not less than 4,880 U.S.P. units of vitamin A per gram and of not less than 640 U.S.P. units of vitamin D per gram.

**Physical Properties.**—Burbot liver oil is a pale, yellow, oily liquid. It has a slightly fishy, but not rancid, odor and a fishy taste. It is soluble in benzene, carbon disulfide, chloroform, ether and ethyl acetate and is slightly soluble in alcohol.

**Actions, Uses and Dosage.**—See the monographs on oleovitamin A and calciferol.

ROWELL LABORATORIES, INC., DIVISION OF BURBOT LIVER PRODUCTS COMPANY

**Burbot Liver Oil:** 60 and 240 cc. bottles.

**Capsules Burbot Liver Oil:** 0.5 cc. adjusted to have a potency of not less than 2,215 U.S.P. units of vitamin A and 315 U.S.P. units of vitamin D per capsule.

**CONCENTRATED OLEOVITAMIN A AND D-U.S.P.**—"Concentrated Oleovitamin A and D is either fish liver oil, or fish liver oil diluted with an edible vegetable oil, or a solution of Vitamin A and D concentrates in fish liver oil or in an edible vegetable oil.

The Vitamin A is obtained from natural (animal) sources or from synthetic Vitamin A or its fatty-acid esters and the Vitamin D may be from natural (animal) sources or may be synthetic oleovitamin D. Concentrated Oleovitamin A and D contains in each gram not less than 50,000 and not more than 65,000 U.S.P. units of Vitamin A, and not less than 10,000 and not more than 13,000 U.S.P. units of Vitamin D." *U.S.P.*

**Physical Properties.**—Concentrated oleovitamin A and D is a thin, oily liquid which may have a fishy, but not a rancid, odor and taste.

**Actions, Uses and Dosage.**—See the monographs on oleovitamin A and calciferol.

#### McKESSON & ROBBINS, INC.

**Concentrated Oleo Vitamins A and D:** 6 cc. vials. A concentrate of vitamins A and D prepared from cod liver oil, the concentrate containing not less than 60,000 U.S.P. units of vitamin A and not less than 10,000 U.S.P. units of vitamin D per gram.

#### WALKER LABORATORIES, INC.

**Drops Concentrated Oleo Vitamin A and D:** Each gram contains not less than 62,500 U.S.P. units of vitamin A and not less than 10,000 U.S.P. units of vitamin D. Natural esters of vitamin A (distilled from fish liver and vegetable oils) plus activated ergosterol in refined corn oil. Flavored with cinnamon.

**PERCOMORPH LIVER OIL.**—*Oleum Percomorphum.*—A blend of the fixed oils obtained from the fresh livers of the percomorph fishes, principally *Xiphias gladius*, *Pneumatophorus diego*, *Thunnus thynnus* and *Stereolepis gigas*—sometimes also *Neothunnus macropterus*, *Katsuwonus pelamis*, *Sarda chiliensis*, *Germo alalunga*, *Thunnus orientalis*, *Scomber scombrus*, *Seriola dorsalis*, *Lutianus campechanus*, *Epinephelus morio*, *Roccus lineatus*, *Cynoscion nobilis*, *Eriscion macdonaldi*, *Epinephelus analogus*, *Stereolepis ishinagi* and *Sphyræna argentea*. Percomorph-liver oil may be blended with 50 per cent of other fish liver oils. It has a potency of not less than 60,000 U.S.P. units of vitamin A per gram and of not less than 8,500 U.S.P. units of vitamin D per gram.

**Physical Properties.**—The material is a yellow to brownish yellow, oil liquid with a fishy taste and odor. It is soluble in benzene, carbon disulfide, chloroform, ether and ethyl acetate and slightly soluble in alcohol.

**Actions, Uses and Dosage.**—Same as those of cod liver oil. See the monographs on oleovitamin A and calciferol.

#### AMERICAN PHARMACEUTICAL COMPANY, INC.

**Oleum Percomorphum, Codanol Brand, with Other Fish Liver Oils and Viosterol:** 10 cc. and 50 cc. A source of vitamin A and D in which not less than 50 per cent of the vitamin content is derived from the liver oils of percomorph fishes with viosterol added. Each gram contains not less than 60,000 U.S.P. units of vitamin A and 8,500 U.S.P. units of vitamin D.

**MEAD JOHNSON & COMPANY**

**Capsules Oleum Percomorphum with Other Fish Liver Oils and Calciferol:** Each capsule contains 83 mg. of percomorph with other fish liver oils and calciferol and supplies a potency of 5,000 U.S.P. units of vitamin A and 700 U.S.P. units of vitamin D.

**Oleum Percomorphum with Other Fish Liver Oils and Calciferol:** 10 cc. and 50 cc. bottles. A blend of percomorph liver oil with other fish liver oils and calciferol which contains not less than 60,000 U.S.P. units of vitamin A and 8,500 U.S.P. units of vitamin D in each gram.

**Other Mixed Vitamin Preparations**

**HEXAVITAMIN-U.S.P.**—"Hexavitamin Capsules [and Tablets] contain in each capsule [or tablet] not less than 5,000 U.S.P. units of vitamin A from natural (animal) sources, or from synthetic vitamin A or its fatty-acid esters, 400 U.S.P. units of vitamin D from natural (animal) sources, or as calciferol or activated 7-dehydrocholesterol, 75 mg. of ascorbic acid, 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin and 20 mg. of nicotinamide." U.S.P.

**Actions, Uses and Dosage.**—For prophylaxis and treatment of conditions arising from deficiency of vitamin A, vitamin D, ascorbic acid, thiamine, riboflavin and nicotinic acid, see the monographs on the various vitamins concerned.

**THE WM. S. MERRELL COMPANY**

**Tablets Hexavitamin:** Each tablet contains 5,000 U.S.P. units of vitamin A, 400 U.S.P. units of vitamin D, 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin, 75 mg. of ascorbic acid and 20 mg. of nicotinamide.

**WALKER LABORATORIES, INC.**

**Capsules Hexavitamin:** Each capsule contains 5,000 U.S.P. units of vitamin A, 400 U.S.P. units of vitamin D, 2 mg. of thiamine, 3 mg. of riboflavin, 75 mg. of ascorbic acid and 20 mg. of niacinamide.

**TRIASYN B** (See under mixed vitamin B components.)



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COLUMBUS PHARMACAL COMPANY, THE, 326-336 Oak St., Columbus 15, Ohio.—Pyramal Maleate, 15.

COMMERCIAL SOLVENTS CORPORATION, 17 E. 42nd St., New York 17, N. Y.—Bacitracin, 129; Choline Gluconate, 492; Expandex, 250; Kwell, 76; Potassium Penicillin G, 150; Procaine Penicillin G, 154.

CONTRA COMPANY, DIVISION OF SEVERNA LABORATORIES, INC., Box 386, Union, N. J.—Contra Applicator, 316; Contra Creme, 316; Contra Diaphragm, 316.

COOPER, WILLIAM, & NEPHEWS, INC., Cooper Building, 1909-25 Clifton Ave., Chicago 14, Ill.—Enbin, 73.

COURTLAND LABORATORIES, 1600 N. Bonnie Beach Pl., Los Angeles 33, Calif.—Normal Human Plasma, 247.

CUTTER LABORATORIES, Fourth and Parker Sts., Berkeley 1, Calif.—Anti-pertussis Serum, 455; Diphtheria and Tetanus Toxoids, Alhydrox, 464; Diphtheria Toxoid, Alhydrox, 459; Dip-Pert-Tet, 470; Dip-Pert-Tet, Alhydrox, 472; Diphtheria, 469; Diphtheria, Alhydrox, 470; Fibrin Foam and Thrombin, 263; Immune Serum Globulin, 457; Normal Human Plasma, 247; Normal Human Serum Albumin, 246; Pertussis Vaccine, 466; Pertussis Vaccine, Aluminum Hydroxide Adsorbed, 468; Tetanus Toxoid, 460; Tetanus Toxoid, Alhydrox, 462.

DIRECT LABORATORIES, INC., 377 Genesee St., Buffalo 4, N. Y.—Calcium Levulinate, 485; Mannitol Hexanitrate, 286.

DOAK PHARMACAL COMPANY, INC., 11 W. 42nd St., New York 36, N. Y.—Salinidol, 54.



- DRUG PRODUCTS COMPANY, INC., THE, 360 Glenwood Ave., East Orange, N. J.—Diethylstilbestrol, 417; Nicotinamide, 555; Nikethamide, 312; Thiamine Hydrochloride, 564.
- DUBIN, H. E., LABORATORIES, INC., 250 E. 43rd St., New York 17, N. Y.—Aminophylline, 358.
- DUREX PRODUCTS, INC., 684 Broadway, New York, N. Y.—Durex Diaphragms, Diaphragm Introducer and Fitting Rings, 317; Lactikol Creme, 316; Lactikol Jelly, 316; Lactikol Metri-Dose Applicator, 317; Lactikol Plunger Applicator, 317.
- DWIGHT, R. E., & COMPANY, 505 35th St., Des Moines 12, Ia.—Ascorbic Acid, 568; Menadione, 577; Potassium Penicillin G, 150; Procaine Penicillin G, 154; Sodium Penicillin G, 156; Thiamine Hydrochloride, 565.
- EATON LABORATORIES, INC., 17 Eaton Ave., Norwich, N. Y.—Aspogen, 380; Furacin, 62; Furadantin, 95; Lorphyn Jelly, 317; Lorphyn Jelly Applicator, 317; Lorphyn Suppositories, 321; Tripazine, 118.
- ELDER, PAUL B., COMPANY, Bryan, Ohio.—Aminophylline, 359; Pyrilamine Maleate, 15.
- ENDOCRINE COMPANY, 4407-09 Park Ave., Union City, N. J.—Thiamine Hydrochloride, 565.
- ENDO PRODUCTS, INC., 84-40 101st St., Richmond Hill 18, N. Y.—Aminophylline, 359; Ascorbic Acid, 568; Balarsen, 181; Cumertilin, 351; Cumertilin Sodium, 351; Diethylstilbestrol, 417; Entromone, 442; Hycodan Bitartrate, 25; Hyflavin, 561; Lauron, 537; Menadione, 577; Mesopin, 190; Niadrin, 88; Nicotinic Acid, 557; Nikethamide, 312; Norodin Hydrochloride, 225; Pyridoxine Hydrochloride, 559; Riboflavin, 562; Sodium Ascorbate, 570; Sodium Morrhuate, 506; Thiamine Hydrochloride, 565; Tubocurarine Chloride, 523.
- ERBA, CARLO, INC., 322 E. 44th St., New York 17, N. Y.—Aminophylline, 359; Progesterone, 424; Sodium Ascorbate, 570; Testosterone Propionate, 449.
- ESTRO CHEMICAL COMPANY, INC., 158 E. 126th St., New York 35, N. Y.—Aminophylline, 359; Diethylstilbestrol, 417.
- ETHICON SUTURE LABORATORIES, New Brunswick, N. J.—Bio-Sorb, 504; Gamphen, 59.
- EVRON COMPANY, INC., THE, 3542 N. Clark St., Chicago 13, Ill.—Aminophylline, 359; Potassium Penicillin G, 150.
- FIRST TEXAS CHEMICAL MFG. COMPANY, P. O. Box 5026, Dallas, Tex.—Glynazan, 366.
- FLINT, EATON & COMPANY, Decatur 60, Ill.—Chothyn Dihydrogen Citrate, 492; Mercuraphylline (Sodium), 353; Nicotinamide, 556; Thiamine Hydrochloride, 565; Trionamide, 118.
- FUNK, CASIMIR, LABORATORIES, INC., 250 E. 43rd St., New York 17, N. Y.—Duo-Sulfanyl, 115; Tri-Sulfameth, 118.
- GANE'S CHEMICAL WORKS, INC., 611-641 Broad St., Carlstadt, N. J.—Phenindione, 261; Secobarbital, 301; Secobarbital Sodium, 301.
- GEIGY PHARMACEUTICALS, DIVISION OF GEIGY COMPANY, INC., 220 Church St., New York 13, N. Y.—Tromexan Ethyl Acetate, 257.
- GOLD LEAF PHARMACAL COMPANY, INC., 36 Lawton St., New Rochelle, N. Y.—Aminophylline, 359; Amphetamine Sulfate, 216; Ascorbic Acid, 569; Corlutone, 424; Diethylstilbestrol, 417; Mephesisin, 513; Para-Pas, 92; Para-Pas Sodium, 93; Sodium Ascorbate, 570; Testosterone Propionate, 449; Thiamine Hydrochloride, 565.

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- HEXAGON LABORATORIES, INC., 3536 Peartree Ave., New York 69, N. Y.—Mephenesin, 513; Para-Aminosalicylic Acid, 92; Sodium Para-Aminosalicylate, 93.
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- HOLLAND-RANTOS COMPANY, INC., 145 Hudson St., New York 13, N. Y.—Koromex Cream, 317; Koromex Diaphragm, 318; Koromex Jelly, 317; Koromex Vaginal Applicator, 318.
- HOMEMAKERS' PRODUCTS CORPORATION, 380 Second Ave., New York 10, N. Y.—Diaparene Chloride, 85.
- HORTON & CONVERSE, 621 W. Pico Blvd., Los Angeles 15, Calif.—Thiamine Hydrochloride, 565.
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- JACKSON-MITCHELL PHARMACEUTICALS, INC., 10401 W. Jefferson Blvd., Culver City, Calif.—Thylose Sodium, 385.
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- LLOYD & DABNEY COMPANY, INC., 412 Central Ave., Cincinnati 2, Ohio.—Sulfaloid, 118.
- LOBICA-DEBRUILLE, INC., 1841 Broadway, New York 23, N. Y.—Metione, 480.
- MACALLISTER LABORATORY, 9213 Wade Park Ave., Cleveland 6, Ohio.—Al-U-Creme, 375.



- MALLARD, INC., 3021 Wabash Ave., Detroit 16, Mich.—Aminophylline, 360; Sulfadiazine, 101.
- MALLINCKRODT CHEMICAL WORKS, Second and Mallinckrodt Sts., St. Louis 7, Mo.—Hippuran, 338; Mandelic Acid, 90; Urokon Sodium, 342; Zinc Peroxide Medicinal, 75.
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- MASSENGILL, S. E., COMPANY, Bristol, Tenn.—Aminophylline, 360; Calcium Levulinate, 485; Hexestrol, 419; Mersalyl and Theophylline, 355; Methadone Hydrochloride, 22; Pasem Sodium, 94; Semikon Hydrochloride, 13; Semoxydrine Hydrochloride, 225; Sulfamerazine, 104.
- McKESSON & ROBBINS, INC., Bridgeport 9, Conn.—Ascorbic Acid, 569; Oleo Vitamins A and D, 581; Thiamine Hydrochloride, 565.
- McNEIL LABORATORIES, INC., 2900 N. 17th St., Philadelphia 32, Pa.—Butisol Sodium, 294; Mer-Diazine, 116; Metha-Merdiazine, 118; Orestralyn, 411; Sulfadiazine, 101; Syndrox Hydrochloride, 225.
- MEAD JOHNSON & COMPANY, Evansville 21, Ind.—Amigen, 479; Ascorbic Acid, 569; Levugen, 489; Oleum Percomorphum with Other Fish Liver Oils and Calciferol, 582; Protolysate, 479.
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- METROPOLITAN LABORATORIES, INC., 182 South St., Oyster Bay, N. Y.—Testosterone, 445; Testosterone Propionate, 449.
- MEYER CHEMICAL COMPANY, 16361 Mack Ave., Detroit 24, Mich.—Aminophylline, 361; Estrone, 407; Progesterone, 424; Sodium Ascorbate, 571.
- MICHAEL REESE RESEARCH FOUNDATION, 2912 S. Ellis Ave., Chicago 16, Ill.—Human Measles Immune Serum, 455; Human Scarlet Fever Immune Serum, 456; Normal Human Plasma, 248; Normal Human Serum, 248.
- MILLER, E. S., LABORATORIES, INC., P. O. Box 2302, Terminal Annex, Los Angeles 54, Calif.—Aminophylline, 361; Ascorbic Acid, 569; Diethylstilbestrol, 418; Estrone, 407; Hormesteral, 412; Menadione, 577; Neostigmine Methylsulfate, 202; Nikethamide, 312; Pyridoxine Hydrochloride, 560; Sul-Di-Mill, 116; Sulfadiazine, 101; Theophylline Ethylenediamine, 361; Thiamine Hydrochloride, 566; Tolulixin, 513.

- NATIONAL DRUG COMPANY, 4663-85 Stenton Ave., Philadelphia 44, Pa.—Aminonate, 479; Ascorbic Acid, 569; Diphtheria and Tetanus Toxoids, Alum Precipitated, and Pertussis Vaccine Combined, 471; Diphtheria and Tetanus Toxoids Combined, Alum Precipitated, 463; Diphtheria Toxoid, Alum Precipitated, 458; Diphtheria Toxoid, Alum Precipitated and Pertussis Vaccine Combined, 469; Influenza Virus Vaccine, Polyvalent, 465; Mannitol Hexanitrate, 286; Nicotinic Acid, 557; Pertussis Vaccine, 466; Pertussis Vaccine, Alum Precipitated, 467; Resinate, 382; Sodium Morrhuate, 506; Tetanus Toxoid, Alum Precipitated, 461; Thiamine Hydrochloride, 566.
- NEPERA CHEMICAL COMPANY, INC., Nepera Park, Yonkers 2, N. Y.—Mandelamine, 91; Neohetramine Hydrochloride, 16; Pyridine, 89.
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- NOVOCOL CHEMICAL MFG. COMPANY, INC., 2911-23 Atlantic Ave., Brooklyn 7, N. Y.—Amylsine Hydrochloride, 44; Monocaine Formate, 37; Monocaine Hydrochloride, 38.
- OHIO CHEMICAL & SURGICAL EQUIPMENT COMPANY, 1400 E. Washington Ave., Madison 10, Wis.—Cyclopropane, 32.
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- PANRAY CORPORATION, THE, 340 Canal St., New York 13, N. Y.—Isoniazid, 89; Parasal, 92; Parasal Sodium, 94.
- PARKE, DAVIS & COMPANY, Joseph Campau Ave. at the River, Detroit 32, Mich.—Benadryl Hydrochloride, 11; Chloromycetin, 133; Dilantin Sodium, 307; Diphtheria-Tetanus Toxoids Combined, 463; Diphtheria-Tetanus Toxoids Combined, Alum Precipitated, 463; Diphtheria Toxoid, Aluminum Phosphate Adsorbed, 459; Etamon Chloride, 212; Mapharsen, 182; Metopon Hydrochloride, 28; Nicotinic Acid, 557; Oral Sodium, 295; Oxycel, 265; Pertussis Vaccine, 466; Phemerol Chloride, 83; Pitressin Tannate, 440; Potassium Penicillin G, 150; Procaine Penicillin G, 155; Sodium Ascorbate, 571; Sulfadiazine, 101; Sulfamerazine, 104; Surital Sodium, 303; Theelin, 407; Theelol, 404; Thrombin, 266; Tuberculin, Purified Protein Derivative, 474; Tyrothricin, 50.
- PASADENA RESEARCH LABORATORIES, INC., 2107 East Villa, Pasadena 8, Calif.—Thiamine Hydrochloride, 566.
- PATCH, E. L., COMPANY, THE, Stoneham 80, Mass.—Alzinox, 380; Glythionate, 366.
- PENICK, S. B., & COMPANY, 50 Church St., New York, N. Y.—Tyrothricin, 50.
- PFIZER LABORATORIES, DIVISION OF CHAS. PFIZER & COMPANY, INC., 630 Flushing Ave., Brooklyn 6, N. Y.—Bacitracin, 130; Dihydrostreptomycin Sulfate, 163; Magnamycin, 131; Polymyxin B Sulfate, 160; Potassium Penicillin G, 150; Procaine Penicillin G, 155; Streptomycin Sulfate, 166; Terramycin, 138; Terramycin Hydrochloride, 140.
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**PHYSICIANS' DRUG & SUPPLY COMPANY**, Third and Callowhill Sts., Philadelphia 6, Pa.—Aluminum Hydroxide, 375; Aminophylline, 361; Amphetamine Sulfate, 216; Ascorbic Acid, 569; Choline Dihydrogen Citrate, 492; Diethylstilbestrol, 418; Folic Acid, 554; Hexestrol, 419; Mannitol Hexanitrate, 286; Methyltestosterone, 445; Niacin, 557; Niacinamide, 556; Propylthiouracil, 484; Pyridoxine Hydrochloride, 560; Riboflavin, 562; Stangen Maleate, 15; Sulfadiazine, 101; Sulfamerazine, 104; Sulmeradine, 116; Testosterone Propionate, 449; Thiamine Hydrochloride, 566; Thimecil, 482; Tolansin, 513.

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**RAYMER PHARMACAL COMPANY**, N.E. Corner Jasper and Willard Sts., Philadelphia 34, Pa.—Aminophylline, 361; Doxyfed Hydrochloride, 226; Mannitol Hexanitrate, 286; Mephesisin, 513; Propylthiouracil, 484; Pyrilamine Maleate, 15; Ray-Tri-Mides, 119; Vitamin B<sub>12</sub>, 551.

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**RORER, WILLIAM H., INC.**, Drexel Building, Fifth and Chestnut Sts., Philadelphia 6, Pa.—Aluminum Hydroxide, 375; Aminophylline, 362; Anadol, 54; Carfusin, 61; Diethylstilbestrol, 418; Disulfyn, 116; Mannitol Hexanitrate, 286; Sodium Ascorbate, 571; Sulfadiazine, 101; Thiamine Hydrochloride, 566; Thylogen Maleate, 15; Vitamin B<sub>12</sub>, 551.



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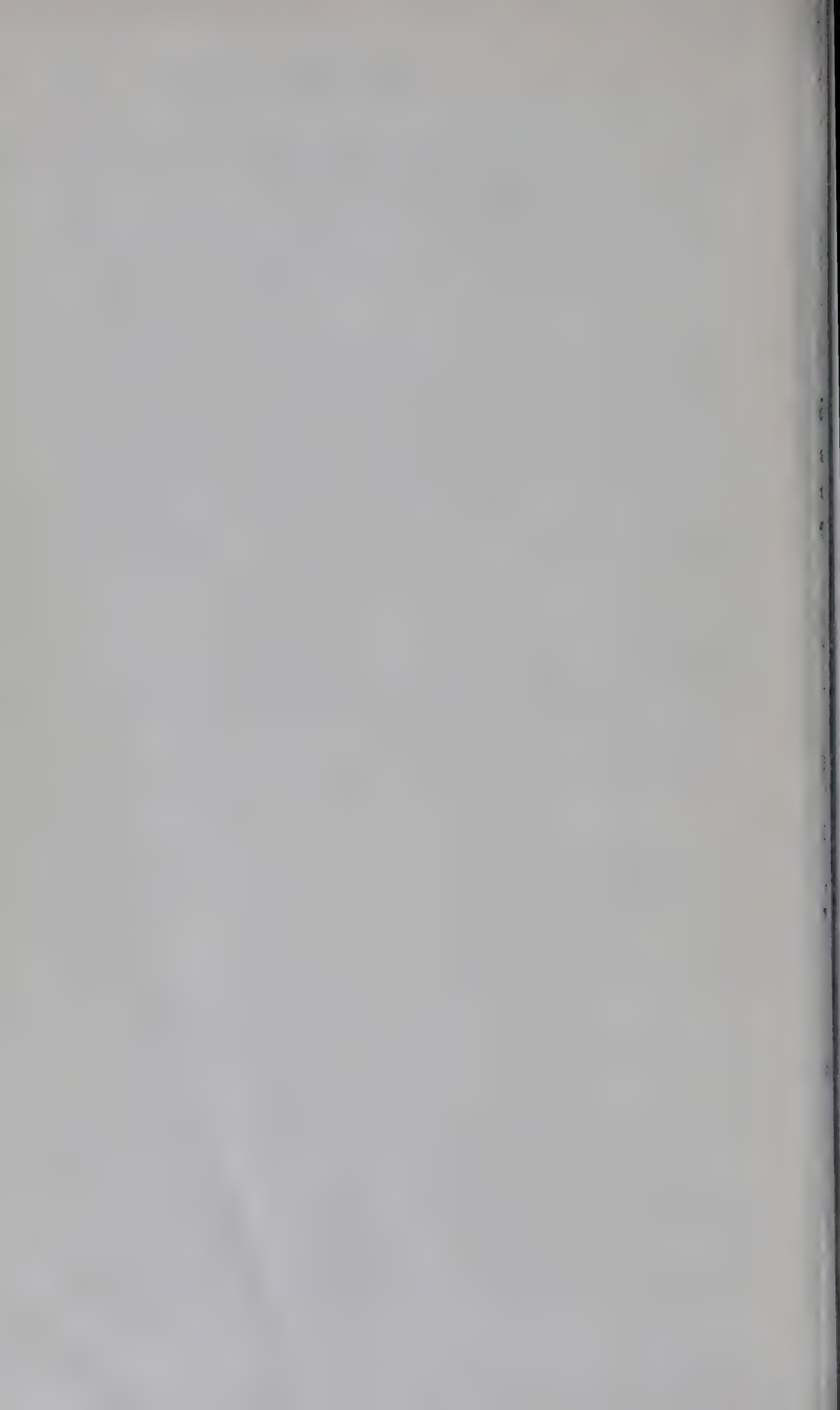
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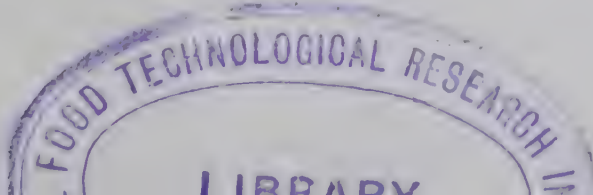
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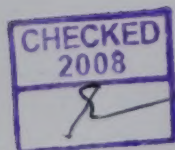








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